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EVALUATION OF THE EFFECTIVENESS OF THERAPEUTIC MEASURES AGAINST PRIMARY TUBERCULOSIS

CONSIDERATION OF SOME LEADING PRINCIPLES

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When the effectiveness of a form of treatment r a certain disease is to be evaluated, there really no other way of doing this than by mparing the results achieved with this treatent in the cases in one group with the course the disease in another group in which the eatment in question has not been used. Before e evidence from such a comparison can be nsidered conclusive, however, it is essential that e two groups be homogeneous in all other reects except the factor under examination—or least as nearly alike as it is possible to achieve th biologic material—and also that the number individuals available for study should be sufiently large and approximately the same in e two groups. In order to be able to eliminate screpancies in the two groups to be compared, is necessary for the examiner to have a thorgh knowledge of the course usually followed the disease in question in all its phases and so to know which are the factors likely to affect is course.

In a disease such as primary tuberculosis in ildren there are a number of factors which ve a considerable influence on the course and e prognosis and which must be carefully borne mind when the cases are being distributed tween the two groups and the results of treatent are to be assessed.

One of these factors is the age of the child hen the infection occurred or when the disease ade its first appearance. The younger the child ring the infant and preschool age, the greater the risk that the course will be malignant, fact reflected in the mortality rate which varies th different ages (table 1).

Consequently, it is not possible, for instance, study the effectiveness of a form of treatent applied to infants over 1 year of age with e course of untreated tuberculosis in infants unger than 1 year of age. It is just as impossible to draw conclusions regarding the inadequacy of certain therapeutic measures against tuberculosis by comparing the course of the disease in patients receiving treatment in the early infant stage with the course in tuberculous infants in whom the disease developed after the age of 1 year. The significance of the age factor in tuberculosis is, however, so widely acknowledged and so obvious that it is seldom overlooked.

TABLE 1.—*Mortality Rate by Age Groups*

Age Group, Years	Children, Number	Mortality Rate, %
0 to 1	39	35.9
1 to 3	64	15.6
3 to 7	225	4.4
7 to 16	125	0.8

Another important factor affecting the prognosis, a factor not always taken into consideration, is the age of the tuberculous infection. If a study is made of the magnitude of the death risk in relation to the time when the tuberculous infection manifests itself, it will be found that in children of the same age group the decrease runs in the main parallel to the length of time which has elapsed since the child's reaction to tuberculin became positive. When the primary focus is calcified, the risk that the disease will end in death during childhood is practically nonexistent, while for infants with the acute febrile form of clinically established primary tuberculosis it is considerable. Since the age factor is such a dominant feature, the age of the tuberculous infection is of greatest significance in the case of young infants (table 2).

TABLE 2.—*Interval Between Manifestation of Primary Tuberculosis and Death*

Interval, Months	Infants, Number
1	4
2	5
3	3
4	1
5	1
6	1

From the Pediatric Clinic of the Caroline Medical stitute at Norrtull's Hospital, Stockholm, Sweden.

Strangely, it seems as though the distribution of the local process in the lungs in primary tuberculosis, as it appears on the roentgenogram, is of less significance to the subsequent course. In all probability this is to be explained by two different circumstances. The anatomic foundation underlying the roentgenologic changes, "the infiltrate," or the lesions in the parenchyma can hardly be determined in the living patient. It may, for instance, be a matter of gelatinous caseous pneumonia, absorbable epituberculosis or atelectasis. The last-mentioned condition is an extremely common one. Owing to its extent, an atelectasis often appears on the roentgenogram as a very serious process, although the underlying tuberculosis of the lung may in actual fact be extremely mild. In my own experience atelectasis is especially likely to occur when the primary tuberculosis is a couple of months old.

Another circumstance reducing the prognostic value of extensive roentgenologic changes in the lungs is the fact that it is not as a rule because of the progression of the primary condition in the lungs that the child dies; death occurs more as a result of the early postprimary diseases meningitis and miliary tuberculosis. Among 104 young infants who died of tuberculosis, progressive primary tuberculosis of the lungs was the cause of death for only 17 of them. It is even more unusual for older children. Almost without exception, when children with primary tuberculosis in the preschool age die of tuberculosis, death is due to meningitis or miliary tuberculosis.

In any case, the child's age at the time of infection and the age of the infection when the child is examined are of far greater prognostic significance than the extent of the roentgenologic lesions in the lungs. Even a very small area of density in the hilus in a young infant with newly manifested primary tuberculosis implies a greater risk to the child than large "infiltrations" in older children six months after the appearance of the tuberculosis.

As is well known, tubercle bacilli can in many instances be demonstrated in fluid obtained by gastric lavage from children with primary tuberculosis. This observation is commonest in infants with absolutely fresh tuberculosis and rarest among older children with a calcified primary focus. As the prognosis with regard to primary tuberculosis is at the same time least favorable for patients in the former category and as the disease is nearly always benign in patients in the latter category, it would seem logical to expect that some indication as to the prognosis could be obtained without the evidence furnished by the gastric lavage. This is a deceptive gui to rely on, however. Among school childr with absolutely fresh primary tuberculosis t bercle bacilli occur in about 50 per cent, and y despite this fact, the prognosis of the disease extremely favorable. Furthermore, the examin tion is sketchy and likely to give rise to erro in consequence of which a negative sample giv little information and in the cases in whi positive samples are obtained it is often necessa to take as many as three or four separate samp of gastric lavage fluid before tubercle bacilli c be demonstrated. In view of all this, the findi of bacilli in the gastric lavage fluid is therefo of little use for prognostic purposes.

Many observers have maintained that a nu ber of other factors, such as the inherited p disposition, the bodily constitution and the mas iveness of the exposure to infection, can influen the prognosis, but such factors are vague a difficult to define with any degree of certaint

On the basis of what has been said, the leadi principles for the evaluation of the effectivene of a method of treatment for primary tuberc losis in children can be stated as follows: 1. T two groups to be studied should comprise a lar number of individuals, about the same numb in each group. 2. The children in the two grou must belong to the same age class. 3. The a of the tuberculous infection must be the sa in the two groups. 4. There should be no esse tial differences between the two groups wi respect to the size of the primary focus, t heredity and constitution of the children and t intensity of exposure.

The importance of making sure that the grou under examination are comparable when a fo of treatment is to be judged is not always o served; this statement is well illustrated by recent article by Levine,[1] in which he assert that rest and confinement to bed have no effe on the course of primary tuberculosis. He co pared primary tuberculosis in infants lying bed with the same disease in children over t infant age who, in contrast to those in the form group, were allowed to get up after the te perature had dropped. He regarded the firs mentioned infants as having received the regul tion treatment of rest and confinement to be It obviously is not possible to draw any co clusions either in a positive or in a negati direction as to the part played by rest by com paring the mortality and incidence of comp cations in two such heterogeneous groups. Ev

1. Levine, M. I.: Primary Tuberculosis: Effe of Unrestricted Activity on Prognosis, Am. J. Di Child. 68:385-389 (Dec.) 1944.

there existed a specific and generally effective treatment for tuberculosis and it were to be used for infants but not for a control series of older children, it would undoubtedly be found that the disease took a more malignant course among a higher proportion of the former category owing to the age factor, which is of such dominant importance for the prognosis. Not even from Levine's paper, therefore, is it possible to reach any conclusion as to whether or not rest is an unnecessary precautionary measure in the treatment of primary tuberculosis in children.

It is not absolutely clear from Levine's article whether in all the cases of primary tuberculosis included in his investigation the diagnosis was made precisely at the time when the disease manifested itself, during the acute febrile stage. If the tuberculous children studied by Levine had not been followed from the time of manifestation (onset of the initial fever; turning point of the sensitivity to tuberculin from negative to positive), then this also constitutes a highly important source of error when the effect of rest on the course of the disease was being assessed. A statement in the article would seem to indicate fairly plainly that the disease had not been diagnosed at its earliest stage in some of the children in the older age group. Levine reported that the tuberculous foci had become calcified and calcification was already visible after as short a time as seven to eight months on an average in the children who had been allowed unrestricted activity with respect to rest; this must mean that in a goodly number of the cases the patient's primary focus had become calcified at a much earlier stage—in other words, soon after the patient came under observation. This implies, on the other hand, that the disease in these cases was not absolutely fresh when it was discovered.

Levine stated that treatment for primary tuberculosis should be given in the same way as for all other infantile infectious diseases—that the child should be kept in bed only during the days of weeks it has an elevated temperature. But the infectious diseases usually treated in this manner? Is a child with acute pneumonia allowed to get up immediately after the crisis—in other words, while the parenchymal infiltration is still present in a practically unchanged condition? Does one allow a child suffering from rheumatic fever with or without demonstrable cardiac involvement to leave his bed as soon as the temperature drops? Certainly not. Instead the child is made to rest until the general condition shows a distinct turn for the better or the abnormalities due to the infection have entirely disappeared and until one feels convinced that signs of active infection are no longer present, the aim of this measure being to reduce the risk of permanent damage to the heart.

One can take an example from the field of infantile tuberculosis itself. Tuberculous exudative pleurisy is a benign disease marked by fever lasting as a rule for a couple of weeks. During the lytic fall in the temperature there is always exudate present and the child may still have difficulty in breathing on account of the constricting effect caused by the exudate in the thorax. If the child, which at this stage still has a high sedimentation rate, is allowed to move about without any restriction, the result is generally that it becomes tired, listless and pale, loses its appetite and loses weight. The same thing is often observed in cases in which acute primary tuberculosis has not been diagnosed but the disease has been interpreted instead as a common infection and the child allowed to run about freely after the temperature has fallen and also in cases in which more rest has been ordered but the order has not been observed. When these children visit the hospital for reexamination they often present the general symptoms mentioned and from the point of view of health cannot be compared with the children who had rested and taken certain other hygienic precautions until the effect of the tuberculous infection on the organism had abated.

Levine has stated that the virulence of tubercle bacilli is in all probability the same in Sweden as it is in the United States. This is quite likely. The virulence of an agent is, however, not a question merely of degree of toxicity of the infective agent in itself but a question of the relation between this toxicity and the sensitiveness and the way of reacting of the individual organism. In this respect one has the impression that there are certain differences between American and Swedish children. As examples of this may be mentioned the high incidence of erythema nodosum in Swedish children in connection with the fever stage of primary tuberculosis and the high incidence of exudative pleurisy during the six months immediately subsequent to this stage. Swedish children are possibly more sensitive to tubercle bacilli and their toxin than American children and therefore cannot endure unrestricted activity immediately after the temperature drop as American children, according to the observations of Myers,[2] Levine and others, have been able to do without any ill effects.

2. Myers, V. A., and others: Tuberculosis Among Children and Young Adults, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1938.

It is difficult to find any other explanation of the fact that in America no ill effects on the general condition of the children have been observed when they have been allowed to lead exactly the same life as healthy children immediately after they are free of fever following the intial fever of the primary tuberculosis and while their sedimentation rate is still high.

For Swedish children with acute primary tuberculosis the necessity for rest before the abatement of the disease cannot be circumvented. The Swedish principles for the treatment of primary tuberculosis are possibly too strict to be applied to American children. Levine's investigation, however, does not prove that this is so. The two groups of tuberculous children which he compared were too incommensurable to furnish conclusive evidence.

In order to prove with any degree of certainty that rest therapy is ineffective and superfluous, one could take as a subject for stud tuberculous children at an age when they hav begun to be a little more active—i. e., from abou the age of 2 to 3 years—take as a starting poi the turn in the sensitivity to tuberculin or th onset of the initial fever and then subject ever second child to rest therapy un!l the sediment tion reaction is normal and allow every othe child of the same age immediately after th temperature drops to lead the same unrestricte life as regards rest as healthy children. Whe the number of individuals is sufficiently com prehensive, the two groups can be compare with respect to mortality rate, complications, ge eral condition and so on, at least during the s months immediately following the manifestatio of tuberculosis. With these conditions, a di ference demonstrated between the two group ought to be significant.

GALACTOSEMIA IN AN INFANT WITH CATARACTS

CLINICAL OBSERVATIONS AND CARBOHYDRATE STUDIES

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Among the unusual anomalies of carbohydrate metabolism, the inability to metabolize galactose normally is outstanding because of its serious effects on various structures and functions of the organism. In infants with this anomaly who consume lactose regularly with their milk, high levels of galactose are noted in the blood and galactose is excreted in the urine. Profound nutritional and developmental disturbances, enlargement of the liver and albuminuria accompany this galactosemia. Most of the signs and symptoms disappear when milk is omitted from the diet. The basic disturbance is considered to be localized in the liver; the enlargement and consistency of this organ suggest the presence of a pathologic process in the hepatic tissue. The nature of the pathologic process, the pathogenesis of the disease and the mechanism by which the toxious effects are produced have been intriguing problems to every observer of the disease.

We have recently observed a case of this rare disorder in a young infant, who presented several features not previously reported. Studies of his carbohydrate metabolism were made in an attempt to obtain information on the nature of the physiopathologic changes.

REVIEW OF THE LITERATURE

Galactosemia was called to the attention of American pediatricians by Mason and Turner in 1935.[1] They described an infant whose clinical course was characterized by failure to gain weight, vomiting, lethargy, enlargement of liver and spleen, secondary anemia, melituria and albuminuria. The sugar in the urine was demonstrated to be galactose. Carbohydrate studies revealed the presence of galactose in the blood, while the blood dextrose level was subnormal. Administration of insulin resulted in elevation of the galactose level in the blood, while the dextrose level fell in a normal manner. The abnormal chemical findings, as well as the pathologic clinical signs disappeared when the ingestion of galactose was stopped by replacing the milk in the baby's diet with a soybean preparation which is free of lactose or galactose. The child then developed well, but follow-up studies after several years still demonstrated the lack of tolerance for galactose.

A report of a similar case was published in 1943 by Norman and Fashena.[2] In the older literature 3 cases can be found, of which 1 certainly and 2 possibly belong in the same category. Göppert[3] in 1917 observed a baby, 26 months old when first seen, who in his physical and mental development corresponded to a 6 month old infant and showed physical and urinary signs identical with those of Mason's patient. Additional features of this case were jaundice, which had been present during the first eight months of life, and a history of hepatic disease in siblings. This patient was treated by reducing the milk in his diet drastically and giving most of it in the form of cottage cheese, i. e. after fermentation of the lactose; thereafter his development progressed, although he never reached normal standards. His galactose tolerance, measured by urinary excretion, improved after two years but did not become normal. In another case, reported by Reuss[4] in 1908, the disease occurred in an infant who at the age of 8 months weighed 1,200 Gm. less than at birth, had an enlarged liver and excreted large amounts of galactose. The galactosuria disappeared after omission of milk from the diet. This infant died before further studies were possible; the necropsy revealed typical cirrhosis of the liver. The cirrhosis was thought to have been alcoholic in origin, since the infant had received tea with cognac during the first days of life.

From the Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati College of Medicine.

1. Mason, H. H., and Turner, M. E.: Chronic Galactemia, Am. J. Dis. Child. **50**:359 (Aug.) 1935.

2. Norman, F. A., and Fashena, G. J.: Chronic Hypergalactosemia, Am. J. Dis. Child. **66**:531 (Nov.) 1943.

3. Göppert, F.: Galaktosurie nach Milchzuckergabe bei angeborenem, familiärem, chronischem Leberleiden, Berl. klin. Wchnschr. **54**:473, 1917.

4. von Reuss, A.: Zuckerausscheidung im Säuglingsalter, Wien. med. Wchnschr. **58**:799, 1908.

Fanconi,[5] in 1933, described the case of a 9 year old boy who excreted large amounts of galactose in his urine as long as his diet contained milk. During a galactose tolerance test the child became apathetic and fatigued and examination showed total blood sugar levels up to 466 mg. per hundred cubic centimeters. This child suffered from familial neurofibromatosis (Recklinghausen) and from cataracta zonularis, which was also present in two of his eleven siblings. He was only slightly underdeveloped and not sick; his liver was not enlarged, and his urine did not contain albumin. This case may represent a much milder form of the disease, in spite of the fact that the concentration of sugar in the urine and the proportion of galactose excreted were more than twice as high as in the other cases. The good physical development of the boy makes it doubtful that this case belongs to the group of the infantile galactosemias.

REPORT OF A CASE

J. D., a 7 week old white boy, was admitted to the Children's Hospital on Aug. 11, 1944, with the chief complaints of vomiting and failure to gain weight. He was the first baby of healthy young parents; no metabolic disorders or congenital anomalies were known to have occurred in his family. He had been born at full term, by normal delivery, weighing 3,580 Gm. At the age of 5 days, severe jaundice developed, and he was therefore sent to a hospital, where he remained for three weeks. He suffered from diarrhea and vomiting. After four different formulas had been tried, the baby was discharged and a very dilute skim milk formula was prescribed. With this diet, there was no diarrhea and vomiting was moderate. The jaundice subsided. At home, the baby vomited about twice a day, sometimes his whole meal; vomiting became worse when his mother tried to give him evaporated milk for one day. He always seemed hungry, and he lost weight.

Examination revealed a poorly developed and poorly nourished, lethargic, pale infant who did not appear acutely ill. His weight was 3,325 Gm. and his temperature 37.2 C. (99 F.). His skin was rough, dry, loose and gray; his muscles were flabby. His pupils were wide and reacted to light sluggishly. The ocular fundi could not be visualized, except for a small peripheral zone, because of an anomaly of the refracting media of both eyes. The nucleus of the lens seemed to be more highly refractive than the cortex, a sharp zone of demarcation separating the two layers. The fundus reflex was present; there was no actual opacity. The condition was diagnosed as an early stage of congenital nuclear cataract. The lungs and the heart were normal. The abdomen was soft; the liver was enlarged and was palpable 2 to 3 fingerbreadths below the costal margin; its edge was sharp and its consistency firm but elastic. The spleen was not felt on admission, but later it was palpable just below the costal margin. There were bilateral indirect inguinal hernias and a small umbilical hernia. The extremities were normal. No tendon reflexes could be elicited. Moro and grasp reflexes were weak.

Laboratory Data.—The urine constantly contained albumin (1 to 3 plus) and sugar (1 to 3 plus) and some granular casts in the sediment. Acetone, urobilinogen and bilirubin were absent. The Kahn reaction of the blood was negative. The hemoglobin content was 7.7 Gm. per hundred cubic centimeters; the red blood cells numbered 2,430,000 and the white blood cells 10,300, with a differential count of polymorphonuclears 41 per cent, lymphocytes 50 per cent and monocytes 9 per cent. The blood sugar level determined two to three hours after the last meal was 22 mg. per hundred cubic centimeters; two days later after a fasting period of six hours it was 163 mg. per hundred cubic centimeters. The values for other chemical constituents of the blood serum are listed in table 1.

TABLE 1.—*Values for Chemical Constituents Other than Sugar in the Blood Serum of J. D.*

	During Milk Diet		During Milk-Free Diet	
Nonprotein nitrogen, mg. per 100 cc.	38	28	26	
Cholesterol, mg. per 100 cc.		83		
Total protein, Gm. per 100 cc.	4.2	4.5	5.1	5.2
Albumin, Gm. per 100 cc.		3.2	4.0	3.8
Globulin, Gm. per 100 cc.		1.3	1.1	1.4
Carbon dioxide content, mM/L.		19.8		
Chlorides mEq/L	115	107		
Inorganic phosphorus, mg. per 100 cc.	4.4	5.5	5.6	4.2
Phosphatase, Bodansky units	20.4		11.3	2
Calcium, mg. per 100 cc.	9.2			
Bilirubin, mg. per 100 cc.	0.68			

they were normal except for lowering of the serum proteins and elevation of the phosphatase. The prothrombin time was seventeen seconds (normal), the cephalin flocculation test gave a negative result, and the sulfabromophthalein sodium test showed 4 per cent retention of the dye thirty minutes after injection of 5 mg. per kilogram of body weight. The spinal fluid was clear and slightly yellowish and contained 2 white blood cells per cubic millimeter. Its protein and sugar contents were elevated (see table 3). Roentgenograms of the chest, of the skull and of the long bones showed essentially normal conditions, the only unusual sign being small zones of decreased density at the distal end of the left ulna and the proximal end of the left fibula, such as may be seen in various conditions interfering with normal growth and nutrition.

Course.—On admission, the patient was given a routine evaporated milk formula calculated to satisfy his caloric requirement, orange juice and cod liver oil concentrate. This diet was taken only moderately well; the baby vomited about twice daily. He remained lethargic, cried little and did not move spontaneously. For a few days during the first week he had some generalized edema. He was given three blood transfusions. The lethargy, areflexia and increased spinal fluid protein seemed to point toward a pathologic process in the central nervous system; the enlarged liver, the hypoproteinemia, hyperglycemia and melituria and perhaps the cataracts indicated a metabolic disturbance. As the data from the laboratory accumulated, increasing attention was directed to the constantly elevated sugar content of the blood and urine in the

5. Fanconi, G.: Hochgradige Galaktose Intoleranz bei einem Kinde mit Neurofibromatosis Recklinghausen, Jahrb. f. Kinderh. **138**:1, 1933.

absence of acetonuria or other signs of diabetes mellitus. It was therefore suspected that the excess sugar might not be dextrose. On Aug. 23, 1944, the blood sugar was fractionated into fermentable and nonfermentable components. It was found that of a total sugar content of 206 mg. per hundred cubic centimeters, only 90 mg. was fermentable. The reducing substance in the urine, which was nonfermentable, was subsequently identified as galactose.[6] During the following week, while metabolic studies were carried out, the patient continued to lose weight, reaching a minimum of 110 Gm. on August 30.

On August 30 his formula was changed to a casein hydrolysate preparation with added dextrose and polymers of dextrose,[7] which does not contain lactose or galactose. Within twenty-four hours, reducing substances were no longer found in the urine, the nonfermentable sugar disappeared from the blood and the total blood sugar became normal. The albuminuria disappeared completely seventy-two hours after the last milk meal. The baby took the new formula well and stopped vomiting. He started to gain weight immediately, rapidly at first and later more slowly. During the second and third weeks after the change of formula he apparently had a slight intercurrent infection, with vomiting and poor appetite, but recovered spontaneously. His liver remained enlarged; its size decreased only slightly during the following two months. Ten days after he began to take the milk-free diet, the tendon reflexes were still absent. Thiamine hydrochloride, 5 mg. daily, was then added to his formula; two to three weeks later, knee and ankle jerks became normally active. During the second month on the milk-free diet, the baby became more alert, his cry became vigorous and he smiled and began to be interested in his surroundings. He followed objects with his eyes. Whenever ophthalmoscopic examination was performed, the red fundus reflex was visible, indicating that the cataracts had not progressed to the stage of dense opacities. On October 27, when the pupils were dilated for a final check-up, the cataracts had disappeared completely; there was no anomaly of the refracting media, and the fundi were clearly seen for the first time and were found to be normal.

During the latter part of the patient's stay in the hospital, while he was on the milk-free diet, the carbohydrate tolerance tests were repeated. For four days of his last week in the hospital he was given an evaporated milk formula again. He took this diet poorly, vomited a few times, lost 140 Gm. of weight and appeared hungry, unhappy and listless. He was then put on the lactose-free formula again and sent home, where his diet consisted of the formula, orange juice, cereals, vegetables and vitamin A, D and B supplements. During the first week at home he gained 450 Gm. and later an average of 140 Gm. a week. At the age of 6 months, his physical and mental development still were retarded by about two months. His liver did not reach normal size until he was 9 months old; at that time it still was harder than normal.

TABLE 2.—*Fasting Levels of Dextrose and Galactose* in the Blood of J. D. on Milk-Containing and Milk-Free Diets*

Diet	Date	Dextrose, Mg./100 Cc.	Galactose, Mg./100 Cc.	Total Sugar, Mg./100 Cc.
Milk	8/14	...	...	224
	8/16	...	...	163
	8/19	...	...	170
	8/23	90	116	206
	8/24	74	89	163
	8/25	88	101	189
	8/28	109	112	221
	8/29	131	34	165
	8/30	133	90	223
Milk-free	8/31	96	0	96
	9/14	121	0	121
	9/15	111	0	111
	10/19	92	0	92
	10/26	85	0	85
Milk	10/27	60	91	151

* The sugar determinations were carried out by the micromethod of Folin, modified for use of a photoelectric colorimeter (Notes on Operation of the Evelyn Photoelectric Colorimeter). The sugar was separated in fermentable and nonfermentable fractions according to the method of Somogyi (Somogyi, M.: J. Biol. Chem. 75:3, 1927). As galactose is designated the nonfermentable fraction, minus a blank value of 7 mg. per hundred cubic centimeters, the average amount of nonfermentable reducing substance found in normal blood. As dextrose is designated the fermentable fraction plus the blank value.

As is seen in chart 1, the weight curve declined consistently during periods when milk was offered. During the milk-free periods, a slow, steady gain took place. The blood sugar assumed normal values within twenty-four hours after use of milk or galactose was discontinued, and the urine became free of sugar at the same time. Albuminuria, which was present as long as the diet contained milk, decreased within twenty-four hours and disappeared seventy-two hours after administration of galactose was stopped. In the course of the four day test period on milk at the end of October, traces of albumin appeared in the urine after the third day but disappeared twenty-four hours after the termination of the period. In table 2 are recorded the values for fasting blood sugar observed at different times. The dextrose level was always normal, while the total sugar and the nonfermentable blood sugar (called galactose) were elevated considerably as long as the diet contained milk.

6. A specimen of urine was treated with lead acetate to remove interfering substances; the excess of lead was removed with hydrogen sulfide, and further decolorization was effected by treatment with charcoal.

The reduction, by the use of Somogyi's microreagent as employed by Nelson (Nelson, N.: Photometric Adaptation of the Somogyi Method for the Determination of Glucose, J. Biol. Chem. **153**:375 [May] 1944) corresponded to 0.42 Gm. of dextrose per hundred cubic centimeters of urine. The rotation in a 2 decimeter tube with a sodium light was 0.63 degrees to the right. $[\alpha]_D^{20}$ of galactose is 81 degrees. Under the assumption that galactose was present, the observed rotation corresponded to 0.39 Gm. of reducing substance per hundred cubic centimeters, a value in fair agreement with the amount determined by reduction.

Identification: The phenylosazone was prepared from the clarified and concentrated specimen of urine in the usual manner. The crystals appeared after fifteen minutes' heating, as they did when the osazone was prepared from pure galactose. They appeared identical with their own galactosazone. After three recrystallizations they melted constantly at 182 C. and when mixed with a known specimen of galactosazone did not cause any depression of the melting point. Mucic acid was prepared in small amounts by nitric acid oxidation of the urine. A brownish red color like that given by galactose was obtained in the phloroglucin test.

7. Nutramigen (Mead Johnson and Company, Evansville, Ind.).

Table 3 presents results of the spinal fluid examination. It is evident that galactose diffuses into the spinal fluid and reaches a level identical with that in the blood, whereas the usual difference between blood and spinal fluid levels of dextrose was noted. The elevation of spinal fluid protein persisted for at least six weeks after milk had been discontinued.

TABLE 3.—*Dextrose and Galactose in Spinal Fluid and Blood of J. D.*

	Spinal Fluid				Blood		
Date	Dextrose, Mg./100 Cc.	Galactose, Mg./100 Cc.	Total Sugar, Mg./100 Cc.	Protein, Mg./100 Cc.	Dextrose, Mg./100 Cc.	Galactose, Mg./100 Cc.	Total Sugar, Mg./100 Cc.
8/18/44	..	..	104	52	..	..	170
8/24/44	40	82	122	68	74	89	163
10/18/44	58	0	58	52	92	0	92
1/18/45	..	..	34	40			

For four days, from August 25 to August 28, an attempt was made to establish a balance of galactose. Table 4 gives the figures for the intake and output of galactose during this period. The excretion amounted to 15 to 25 per cent of the intake. So far as can be judged from these few figures, utilization of smaller amounts of galactose appears to be no better than that of larger quantities.

Review of Clinical Observations.—In this case there was evidence of widespread damage affecting various organs, as well as general malnutrition and underdevelopment. Enlargement of the liver was the most persistent pathologic feature and was still present, although less prominent, three months after milk had been discontinued. There was only minimal evidence of disturbed hepatic function, except for the specific defect of the galactose metabolism

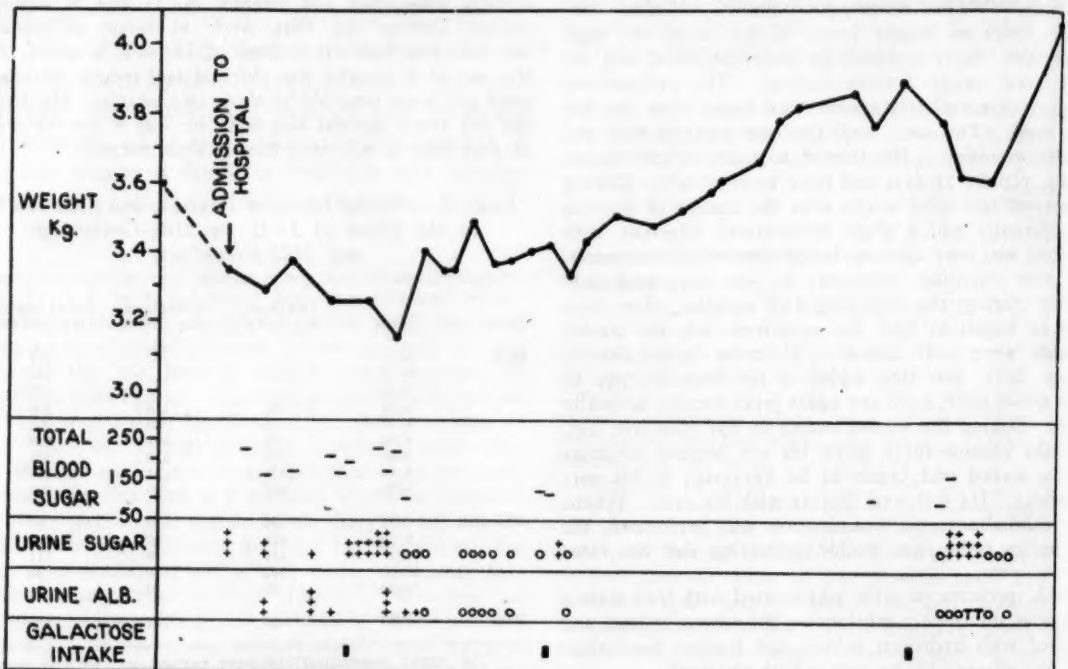

Chart 1.—Weight curve, blood sugar and urinary sugar and albumin in relation to ingestion of galactose during the hospital stay of J. D. The periods of milk diet are marked by a band in the bottom compartment of the chart and administration of galactose for tolerance tests by corresponding short bands in the next higher compartment.

TABLE 4.—*Galactose Balance of J. D. on Milk Diet* *

Date	Intake, Gm.	Urinary Output Gm.	Urinary Output % of Intake	Comment
8/25	13.0	1.97	15.1	Galactose tolerance test
8/26	9-9.5	(1.52)	(16)	24 hour value calculated from 18 hour collection
8/27	10-11	1.76	17	
8/28	5.5-6	1.47	25	Dextrose tolerance test

* The intake of galactose was calculated from the amount of milk formula consumed and retained. A test dose of galactose was added on the first day. The urine was collected quantitatively, except on the second day, when one six hour specimen was lost; for this day, the twenty-four hour output was calculated from the actually determined eighteen hour value.

Renal damage was indicated by the albuminuria and the cylindruria, but the excretory function seemed unimpaired. The disturbance was easily reversible with the cessation of ingestion of galactose. Albumin disappeared from the urine within three days, a decrease being notice-

able after one day. Traces of albumin reappared later when milk was given for three days.

Secondary anemia was pronounced at an age at which nutritional factors do not usually show their effects.

The central nervous system and the eyes exhibited pathologic changes. Lethargy, mental dulness and absence of interest in the surroundings were striking. An additional sign was the absence of the tendon reflexes during the earlier part of the patient's stay in the hospital; these became normal several weeks after the milk had been withdrawn and after thiamine hydrochloride had been added to the diet. The spinal fluid protein was persistently elevated. Early nuclear cataracts were seen; they disappeared within a few weeks.

The presence of cataracts and their disappearance on a milk-free diet are of particular interest. With the exception of Fanconi's case,[5] which may not belong in this group, cataracts have not been described in the galactosemia of human beings.[8] In animals, an effect of galactose on the crystalline lens has been known since 1935, when Mitchell reported her experiments on rats fed on a diet rich in lactose.[9] Some changes in the lenses occurred in all and mature cataracts in a high percentage of these rats. In subsequent studies the author found that galactose was the responsible factor in the diet.[10] The animals had persistently elevated blood sugar values and galactosuria. No pathologic changes other than those in the eyes were noted either in vivo or on postmortem examination.[11] Yudkin and Arnold observed that cataracts develop in young rats more readily and more often show the nuclear form than in old rats.[12] Of the different forms and stages of cataracts described in detail by Mitchell, one corresponds exactly to the picture seen in our patient; the zone of increased refraction surrounding the nucleus. When galactose was omitted from the diet of the rats at different stages of the development of the cataracts, the lenticular changes progressed to complete opacity in all but a few animals; later, some clearing of the periphery took place. In some of the rats in which the lesion did not progress to the stage of complete opacity, the lenses became completely clear.[11] As far as we know, this experiment is the first instance in which cataracts have been shown to regress.

Comment.—In view of the diversity of the pathologic changes, all of which seem to be more or less easily reversible, a discussion of the possible mechanism of their origin seems to be in order. There are several objections to the hypothesis of Mason and Turner that malnutrition and damage to the various organs are due to hypoglycemia, which, in turn, is caused by the presence of galactose in the blood. First, hypoglycemia per se, as seen in glycogen storage disease and hyperinsulinism, does not produce symptoms similar to those of galactosemia. Second, hypoglycemia does not appear to be an essential feature of the disease; in our case, hypoglycemia was not observed except transiently during a galactose tolerance test. The presence of large amounts of galactose in blood and urine appears to be the one observation common to all reported cases and to the reports of experiments on animals. The galactose occurs in the spinal fluid at a level equal to that in the blood. From this fact one may infer that it readily diffuses into other body fluids and tissues. It may be conceived that on some of these tissues, or on all, galactose has a toxic effect. Evidence for a direct toxic effect of galactose on lens tissue was noted by Kirby, Estey and Wiener [13] and by A. Bakker,[14] who observed fine subcapsular densities when he added galactose to the culture medium of rat lenses in vitro. Toxic effects on the nervous system were observed by Lecoq and his associates,[15] who were able to produce *des crises névritiques,* resembling beriberi, in pigeons by substituting galactose for saccharose or dextrose in their otherwise balanced diets. The crises

8. Dr. Mason mentioned in a personal communication that his patient had cataracts, too; this complication was not described in the original report. These cataracts were discovered late in the patient's course; they did not regress and were treated surgically in a conventional manner.

9. Mitchell, H. S., and Dodge, W. M.: Cataract in Rats Fed on High Lactose Rations, J. Nutrition **9**:37 (Jan.) 1935.

10. Mitchell, H. S.: Cataract in Rats Fed on Galactose, Proc. Soc. Exper. Biol. & Med. **32**:971 (March) 1935.

11. Mitchell, H. S., and Cook, G. M.: Galactose Cataract in Rats, Arch. Ophth. **19**:22 (Jan.) 1938.

12. Yudkin, A. M., and Arnold, C. H.: Cataracts Produced in Albino Rats on a Ration Containing a High Proportion of Lactose or Galactose, Arch. Ophth. **14**: 960 (Dec.) 1935.

13. Kirby, D. B.; Estey, K., and Wiener, R. v. E.: Study of Effect of Changes in Nutrient Medium on Lens Epithelium, Cultivated "in Vitro," Tr. Am. Acad. Ophth. **37**:196, 1932.

14. Bakker, A.: Zur Pathogenese der Galaktosekatarakt, Arch. f. Ophth. **140**:531, 1939.

15. Randoin, L., and Lecoq, R.: Influence de la nature des glucides alimentaires sur la production d'états polynévritiques aigus, récidivants ou chroniques, obtenus malgré la présence de levures ou d'extraits de levure, Compt. rend. Acad. d. sc. **185**:1068 (Nov. 14) 1927. Lecoq, R., and Duffau, R.: La guérison du déséquilibre alimentaire glucidique aigu chez le pigeon et sa répercussion sur le métabolisme glucidique musculaire, ibid. **206**:530 (Feb. 14) 1938.

could not be cured and the birds died, even with high doses of brewers' yeast or vitamin B_1, unless galactose was omitted from the food. The histopathologic changes in these pigeons were confined to the peripheral nerves, whereas the central nervous system was apparently intact.

It may seem paradoxic to ascribe toxic properties to a substance which is produced by the mammalian organism for the consumption of the young. However, galactose appears to be metabolized with difficulty. It is believed that the liver alone has the ability to store it and to convert it into dextrose and that it cannot be utilized without being converted in this manner. The ability of the liver to handle galactose is limited; an early manifestation of damage to the liver is its failure to remove galactose from the blood stream. Apparently galactose is excreted in the urine as soon as any considerable amount is present in the circulation.[15a]

The ability of the liver to convert and to store galactose seems to be impaired but not completely lost in galactosemia. The degree of deficiency apparently varies in the different cases and in Mason's and Göppert's cases seemed to diminish after several years. Our patient excreted 15 to 25 per cent of the galactose present in his milk diet; in Göppert's patient the excretion varied from 30 to almost 50 per cent. The remainder of the galactose must have been metabolized or stored. Mason and Turner suggested that large amounts of galactose are stored in the liver as glycogen which is not readily mobilized. The observation of Bell [16] that the glycogen formed in the liver of galactose-fed rabbits has a chain length different from that formed from dextrose may offer a substrate for this assumption. However, no biopsy or necropsy reports are available to substantiate this hypothesis.

Reuss's report [4] contains the only description of a necropsy on a patient who may be strongly suspected of having suffered from galactosemia. The typical picture of Laennec's cirrhosis was found. Goodwin [17] briefly mentioned the case of a patient observed in Baltimore, in whom a malformation of the liver with acinar grouping of the liver cells was present; this case has not been reported in detail. It is difficult to believe that the enlargement of the liver in our case and in the other cases of survival was due to cirrhosis. The apparently good prognosis of the disorder, the minimal impairment of other hepatic functions and the reversibility of the enlargement of the liver do not tend to support such an assumption. The observations of Reuss and Göppert suggest that the dysfunction of the liver which results in galactosemia may be either followed by or associated with cirrhosis or other disease of the liver of the icteric type. With modern therapy, precirrhotic stages of disease of the liver have been shown to regress when the cause was removed; in galactosemia, such a precirrhotic stage may exist, perhaps as the consequence rather than as the pathologic anatomic basis of the physiologic disorder. In Göppert's patient, who was over 2 years old when treatment was started, the process apparently was arrested, but the child never developed normally, an indication perhaps that the damage had progressed beyond complete repair. The observation of galactosemia in very young infants makes it likely that the defect is congenital. That there may be a genetic association of this defect with other diseases of the liver, with varying manifestations in different members of a family, is suggested by Göppert's report.

CARBOHYDRATE STUDIES

Special studies were directed toward evaluating quantitatively the effects of ingestion of galactose and dextrose on the levels of both sugars in the blood of J. D. For the tolerance tests, 1.75 Gm. of carbohydrate per kilogram of body weight was used in each instance.

Chart 2 shows the first galactose tolerance test, which was done on August 25, when the baby was getting an evaporated milk formula. Both the dextrose and the galactose blood levels were near 100 mg. per hundred cubic centimeters in the beginning of the test. After the ingestion of galactose, its level in the blood rose steeply, reaching a maximum of 297 mg. per hundred cubic centimeters after one and a half hours. The fall of the curve was much slower, and after nine hours the level was still considerably above the original one. The dextrose underwent an almost exactly opposite change, although to a smaller degree, with a lag of about one-half hour. After the initial abrupt rise of the curves these opposite movements compensated each other so perfectly that the total blood sugar remained practically constant from the third to the ninth hour. During this test, a minimum dextrose level of 40 mg. per hundred cubic centi-

15a. Deuel, H. J.: Intermediary Metabolism of Fructose and Galactose, Physiol. Rev. **16**:173 (April) 1936.

16. Bell, D. J.: Liver Glycogen in Molecular Structure of Glycogen Formed After Ingestion of Galactose by Fasted Rabbits, Biochem. J. **30**:1612 (Sept.) 1936.

17. Goodwin, T. C.: Anomalies of Carbohydrate Metabolism, in Holt, L. E., and McIntosh, R.: Diseases of Infancy and Childhood, ed. 11, New York, D. Appleton-Century Company, Inc., 1940, p. 1359.

meters was reached after two hours. No symptoms of shock were observed. The galactose tolerance test was repeated twice while the baby was on a milk-free diet, with results essentially similar to those of the first test. In the test presented in chart 3, the opposite movement of the dextrose and galactose curves is evident during the first two hours only; thereafter, the dextrose remained at its low level, between 50 and 60 mg. per hundred cubic centimeters, through the eighth hour, while the galactose fell slowly and after eight hours reached a level only slightly above the patient's usual fasting level when he

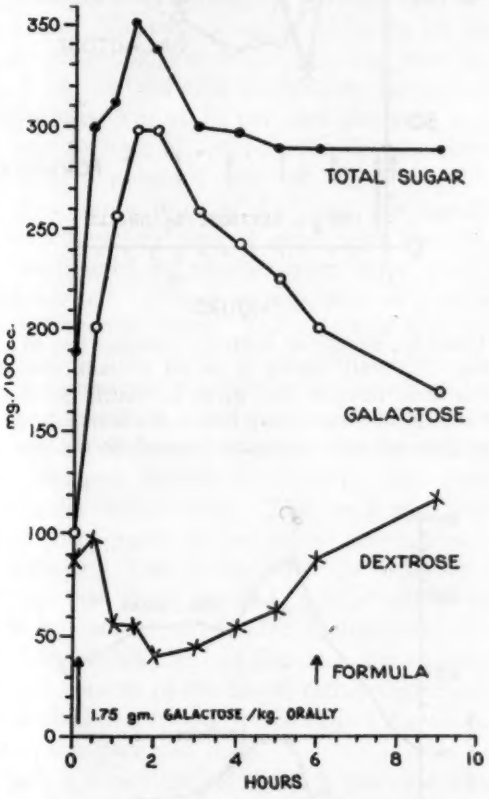

Chart 2.—Results of galactose tolerance test on J. D. (Aug. 25, 1944) during a period of milk diet. The test was started six hours after the last meal; six hours after the beginning of the test, another milk feeding was offered.

was on a milk diet. In this test, the galactose disappeared from the blood within twelve hours, but in all other tests a much longer time was required for its complete elimination.

The galactose in the blood of a normal baby of the same size who was tested as a control reached a maximum level of 56 mg. per hundred cubic centimeters after one hour and disappeared within one and a half hours. No galactose was excreted in the urine (chart 4).

On October 26, when the patient's formula was changed from the special preparation to milk, the levels of both sugars were followed through the first twenty-four hours of the milk diet. The results are given in chart 5. The

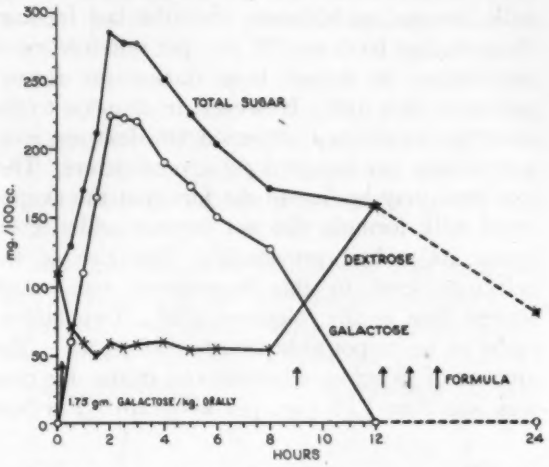

Chart 3.—Results of galactose tolerance test on J. D. (Sept. 15, 1944) during a period of milk-free diet. The test was started three hours after the last meal; the formula offered during the later part of the test contained no carbohydrates other than dextrose and its polymers.

galactose level rose gradually in the first part of each four hour period, to drop slightly at its end to levels still above the initial level of each period. As the next feeding was given, a new rise was superimposed on this higher level, so

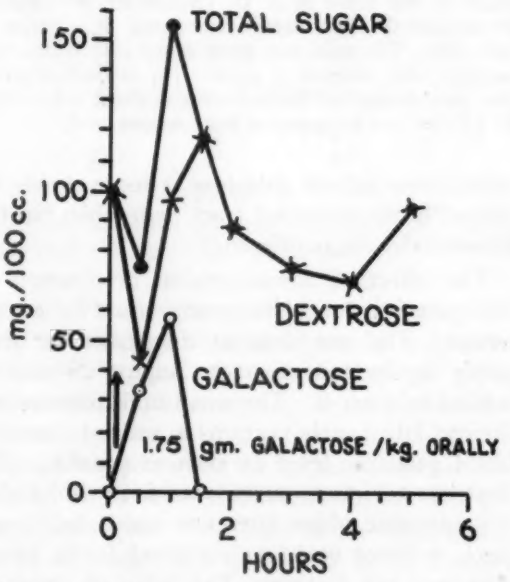

Chart 4.—Galactose tolerance curve for a normal infant of the same weight as J. D.

that the curve assumed a stepladder pattern. The dextrose level showed relatively low postprandial elevations during the first two periods and none after the third one, when the galactose

level reached 100 mg. per hundred cubic centimeters. After the third feeding, the dextrose stayed at a lower level than the galactose. Twenty-four hours after the beginning of the milk diet and eight hours after the last feeding, the galactose level was 90 mg. per hundred cubic centimeters, as it had been during the former period of milk diet. However, in contrast to the observations during that period, the dextrose level was 60 mg. per hundred cubic centimeters. This low level may be due to the fact that the evaporated milk formula did not contain added corn syrup, as it had previously. The rise of the galactose level in this experiment was much slower than in the tolerance tests. Two factors seem to be responsible for the difference. The amount of galactose administered at any one time was less than 1.75 Gm. per kilogram. Further-

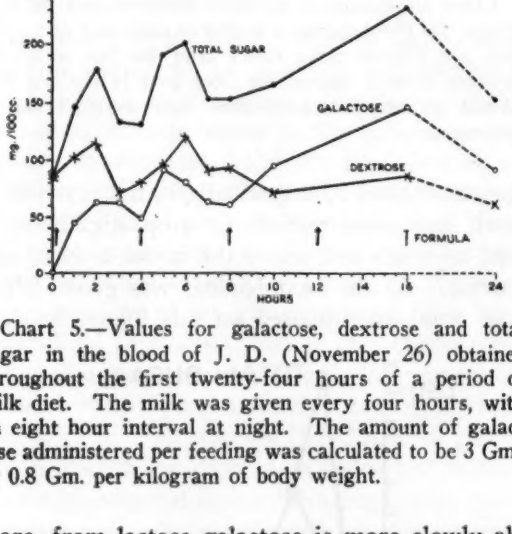

Chart 5.—Values for galactose, dextrose and total sugar in the blood of J. D. (November 26) obtained throughout the first twenty-four hours of a period of milk diet. The milk was given every four hours, with an eight hour interval at night. The amount of galactose administered per feeding was calculated to be 3 Gm., or 0.8 Gm. per kilogram of body weight.

more, from lactose galactose is more slowly absorbed in the intestinal tract than when the free monosaccharide is offered.[18]

The effect of administration of dextrose on the galactose level was studied in two experiments. The test dose of dextrose was given orally in the test done on August 28 and recorded in chart 6. The usual milk formula was divided into hourly portions in order to keep the blood galactose level as even as possible. The dextrose tolerance curve was flat with a deep hypoglycemic phase after one and a half hours. Such a curve could be expected for a patient who was not fasting. The galactose level fell maximally by 36 mg. per hundred cubic centimeters. The milk feeding alone might have been expected to produce a constant or even rising

18. Cori, C. F., and Cori, G. T.: Relation Between Absorption and Utilization of Galactose, Proc. Soc. Exper. Biol. & Med. **25**:402 (March) 1927.

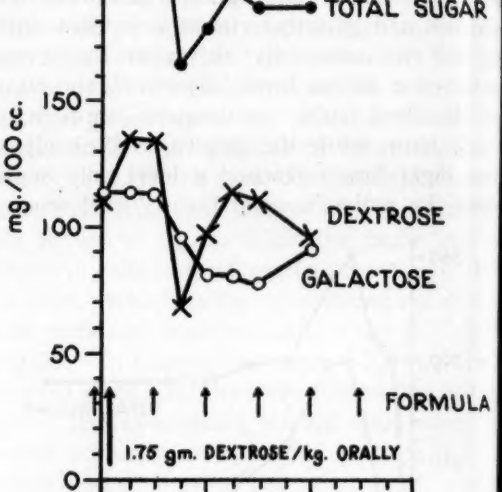

Chart 6.—Results of dextrose tolerance test on J. D. (Aug. 28, 1944) during a period of milk diet. The usual milk formula was given in hourly portions of 30 cc., starting two hours before the administration of the dextrose, and continuing throughout the test.

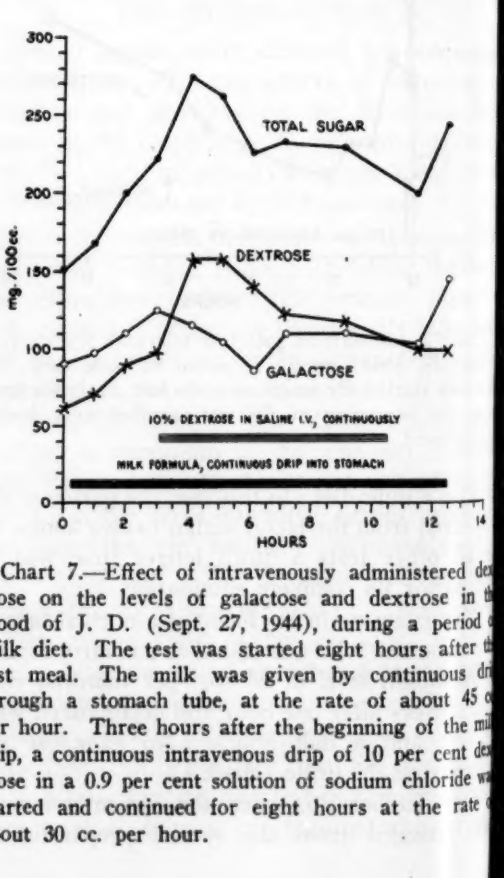

Chart 7.—Effect of intravenously administered dextrose on the levels of galactose and dextrose in the blood of J. D. (Sept. 27, 1944), during a period of milk diet. The test was started eight hours after the last meal. The milk was given by continuous drip through a stomach tube, at the rate of about 45 cc. per hour. Three hours after the beginning of the milk drip, a continuous intravenous drip of 10 per cent dextrose in a 0.9 per cent solution of sodium chloride was started and continued for eight hours at the rate of about 30 cc. per hour.

galactose content of the blood. The results of this test strongly suggest a depressant effect of dextrose on the galactose level. It was desirable to ascertain whether this effect was produced by an action on the intermediary metabolism or by inhibition of the intestinal absorption, since the absorption of galactose is known to be retarded by the simultaneous presence of dextrose in the intestine.[19] In the crucial experiment (chart 7), the factor of intestinal absorption was eliminated by intravenous administration of the dextrose. This time there was an attempt to maintain a constant level of galactose in the blood by dripping the formula through a stomach tube at an even rate. The patient had been fasting for eight hours preceding the test. For the first three hours, he received milk alone; then a continuous intravenous drip of 10 per cent dextrose in 0.9 per cent solution of sodium chloride was administered at a constant rate for eight hours. A blood dextrose level of 158 mg. per hundred cubic centimeters was reached after one hour and maintained for another hour, after which it gradually fell. This is an indication of a normal Staub-Traugott effect. The galactose level rose during the first three hours, when milk alone was administered; this period was apparently too short to establish a constant level. Soon after the infusion of dextrose was started, the galactose level dropped definitely, reaching the lowest value three hours later. This level was maintained throughout the period of administration of dextrose. Two hours after the injection of dextrose had been stopped, the galactose rose by 50 mg. per hundred cubic centimeters. This curve establishes the fact that it is the increased dextrose content of the blood, rather than factors of intestinal absorption, which causes the depression of the galactose level.

Chart 8 shows the results of a dextrose tolerance test performed during the milk-free period. Except for a delayed fall, the curve appears to be normal.

A levulose tolerance test gave results within the normal range; the levulose rose to a level of 5 mg. per hundred cubic centimeters and disappeared from the blood stream rapidly.

Comment.—The most impressive result of the experimental studies of the carbohydrate metabolism in this patient is the demonstration of mutually antagonistic effects of galactose and dextrose. It was observed that the administration of galactose in tolerance tests consistently produced a fall of the dextrose level in the blood (see charts 2 and 3). The reverse effect could be demonstrated when large amounts of dextrose were introduced, either by mouth or by vein (charts 6 and 7). A reciprocal relationship between the levels of galactose and dextrose has been demonstrated by Wagner [20] in galactose tolerance tests on a large number of patients who did not suffer from a specific defect in their galactose metabolism. In these tests it was noted that the higher the galactose levels attained, the greater was the depression produced in the dextrose curve.

Such results seem to indicate that galactose and dextrose may act in a competitive manner on a common metabolic mechanism. This mechanism in all likelihood resides in the liver, the organ concerned with the metabolism of both

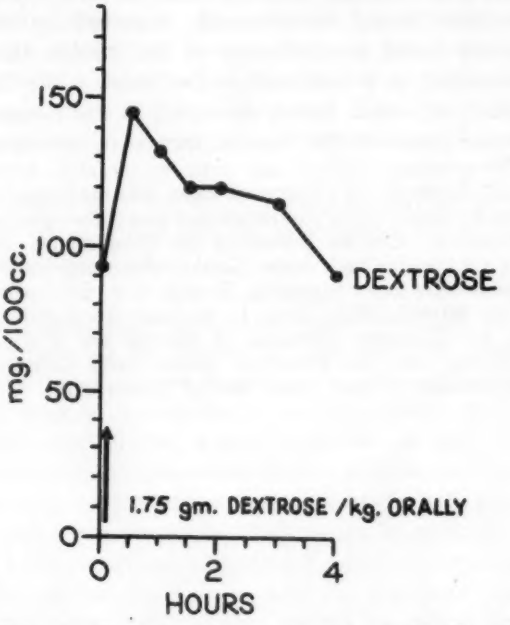

Chart 8.—Dextrose tolerance curve for J. D. (Oct. 19, 1944) during a period of milk-free diet.

sugars. The suggestion of Mason that the blood sugar–lowering mechanism of the body may respond to the level of total blood sugar rather than to that of dextrose may be substantiated if one assumes that it is the liver which responds in such a manner, while the hormonal mechanisms respond to the level of dextrose alone. The primary importance of the liver in the regulation of the blood sugar was established by C. Bernard and has been reemphasized by the work of Mann and Soskin.[21] One may therefore assume that

19. Cori, C. F.: The Rate of Absorption of a Mixture of Glucose and Galactose, Proc. Soc. Exper. Biol. & Med. **23**:290 (Jan.) 1926.

20. Wagner, R.: Galactose Tolerance Test in Endocrine Disorders in Children, Am. J. Dis. Child. **65**:207 (Feb.) 1943.

21. Soskin, S.: The Blood Sugar: Its Origin, Regulation, and Utilization, Physiol. Rev. **21**:140 (Jan.) 1941.

the liver responds directly rather than through a hormonal mediating factor, such as insulin, to the level of the blood sugar. There is additional evidence against the participation of insulin in the galactose metabolism. In diabetic patients, as well as in depancreatized animals, the galactose tolerance curves are usually normal and insulin has little if any effect on the blood galactose level.[22] Mason was able to demonstrate antagonistic changes in the levels of galactose and dextrose in his patient after injection of insulin; in our case only equivocal results were obtained in this test. The rise of galactose which Mason observed may be explained tentatively by assuming an action on the liver alone. It might be that the low blood sugar level resulting from the effect of the insulin stimulates the outpouring of both galactose and dextrose from the liver. The dextrose would be constantly removed by the tissues under the influence of the insulin, thus remaining at a low level in the blood, while the galactose, which is not deposited in the tissues, would remain in the blood in increasing amounts.

22. Kosterlitz, H.: Untersuchungen über die Verwertung der Galaktose in physiologischen und pathologischen Zuständen: über die Bedeutung der Galaktosämie und der Glykosämie nach oraler Galaktosebelastung für die funktionelle Leberdiagnostik, Ztschr. f. d. ges. exper. Med. **90**:465, 1933. Roe, J. H., and Schwartzman, A. S.: Galactose Tolerance of Normal and Diabetic Subjects, and the Effect of Insulin upon Galactose Metabolism, J. Biol. Chem. **96**:717 (June) 1932.

SUMMARY

1. A case of galactosemia in a 7 week old infant was observed. The clinical features were failure to gain and develop normally, vomiting, lethargy, bilateral cataracts, enlargement of the liver and absence of tendon reflexes. Laboratory examinations revealed the presence of large amounts of galactose in the patient's blood, urine and spinal fluid; there were albuminuria, anemia and increase in the spinal fluid protein. All pathologic signs and symptoms, including the cataracts, disappeared gradually after milk was omitted from the diet.

2. Carbohydrate metabolism in the patient was studied by means of tolerance tests, in which galactose, milk formula and dextrose were used. Mutually antagonistic effects of galactose and dextrose were demonstrated; it is assumed that the two sugars may act in a competitive manner on a common metabolic mechanism which resides in the liver.

3. A toxic effect of galactose on the various tissues is suggested as the cause of the extensive pathologic changes noted in the disease.

4. Four or 5 cases of galactosemia were found in reviewing the literature.

5. The disease is probably a congenital anomaly. The few reports available indicate that it may be associated with, or followed by, cirrhosis of the liver.

PRECORDIAL LEADS IN CHILDHOOD

COMMENT ON THE PRESENCE OF DOUBLE UPWARD DEFLECTIONS IN LEADS FROM THE STERNAL REGION OF NORMAL CHILDREN

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PHILADELPHIA

The publication in 1932 of the paper by Wolferth and Wood [1] on the value of chest leads in the diagnosis of coronary occlusion has been followed by numerous studies describing not only variations in the precordial electrocardiogram found in association with coronary occlusion but also similar changes that may result from myocardial damage due to other conditions.[2]

Confusion resulting from the use of varying positions of the chest lead and of the remote electrode by different observers led to the formulation in 1938 [3] and in 1943 [4] of recommendations for standardization of precordial leads by a joint committee of the American Heart Association and of the Cardiac Society of Great Britain and Ireland. It was suggested that electrode connections be so made that relative positivity of the precordial electrode be represented in the finished tracing by an upward deflection, as is the case in standard limb leads, and relative negativity by a downward deflection.

Six precordial points were recommended if multiple electrodes were to be used, the positions to be referred to as C_1, C_2, C_3, C_4, C_5 and C_6. The first of these points is situated at the right margin of the sternum and the second at the left margin of the sternum, both in the fourth interspace. The remaining points lie on a line extending from the second point to the apex, at the level of which the line is continued around the left side of the chest. The third point lies midway between the left sternal margin and the midclavicular line, the fourth point at the midclavicular line, the fifth point at the left anterior axillary line and the sixth point at the left midaxillary line.

In 1938, the use of a single precordial lead was recommended for ordinary purposes, the electrode to be placed on the extreme outer border of the apex regardless of the position of the apex with reference to the bony points of the chest; such a lead was to be known as lead IV. Subsequently, the committee on standardization, agreeing on the inadequacy of a single lead, suggested three precordial leads as the least number to be regarded as suitable for general purposes. The use of the C_1, C_3 and C_5 positions was advised for persons who wished to reduce the number of precordial leads to a minimum. No decision could be reached on the best location for the remote electrode—i. e., whether the precordial electrode should be paired with an electrode on the right arm (CR lead) or on the left leg (CF lead) or with a central terminal connected through equal resistances of 5,000 or more ohms to electrodes on each of the three extremities (V lead). The committee did not feel it desirable to make any recommendations bearing on the question as to whether precordial leads should be taken routinely or in selected cases only.

At the Children's Hospital, precordial leads CF_2 and CF_4 had been taken routinely within recent years whenever the electrocardiographic study of a patient had been requested. In view

From the Department of Pediatrics, University of Pennsylvania School of Medicine, and the Children's Hospital.

1. Wolferth, C. C., and Wood, F. C.: The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads, Am. J. M. Sc. **183**:30, 1932.

2. (*a*) Katz, L. N., and Kissin, M.: A Study of Lead IV: Its Appearance Normally, in Myocardial Disease and in Recent Coronary Occlusion, Am. Heart J. **8**:595, 1933. (*b*) Hoffman, A. M., and Delong, E.: Standardization of Chest Leads and Their Value in Coronary Thrombosis and Myocardial Damage, Arch. Int. Med. **51**:947 (June) 1933. (*c*) Levy, R. L., and Gruenn, H. G.: Precordial Lead of the Electrocardiogram (Lead IV) as an Aid in the Recognition of Active Carditis, Am. Heart J. **10**:881, 1935. (*d*) Master, A. M.; Dack, S.; Kalter, H. H., and Jaffe, H. L.: Significance of the Absent or Small Initial Positive Deflection in the Precordial Lead, ibid. **14**:297, 1937. (*e*) Vander Veer, J. B., and Edwards, J. C.: The Significance of Small and Absent Initial Positive Deflections in the Chest Lead, Am. J. M. Sc. **197**:663, 1939. (*f*) Johnston, F. D.; Rosenbaum, F. F., and Wilson, F. N.: The Ventricular Complex in Multiple Precordial Leads, Mod. Concept Cardiovasc. Dis., 1943, Vol. 12.

3. Standardization of Precordial Leads: Joint Recommendations of American Heart Association and Cardiac Society of Great Britain and Ireland, Am. Heart J. **15**:107 and 235, 1938.

4. Standardization of Precordial Leads (Second Supplementary Report), J. A. M. A. **121**:1349 (April 24) 1943.

of the doubt in the minds of the committee on standardization as to the value of precordial leads in all cases, it seemed advisable to review the changes noted in such leads previously taken at the Children's Hospital, in order to determine if possible whether their routine use should be continued. As an initial study, there is presented in the present paper an analysis of single tracings obtained from the first 150 children whose electrocardiographic examination included precordial leads, excluding only 3 children whose tracings had been taken at a time when they were receiving large amounts of digitalis. When serial tracings had been taken, only the first tracing of the series has been used. One patient had been admitted twice, bringing the total number of tracings up to one hundred and fifty-one. Tracings were taken in the recumbent position, an oscillograph type of electrocardiograph being used.

The ages of these children ranged from 9 days to 15 years, the average age being 7.6 years and the age of greatest frequency 8 years.

Adults.—A fair amount of information is available concerning precordial electrocardiograms of normal adults.[5]

Changes in contour of the tracing may be noted with a shift in position of the electrode on the chest wall. The P wave is usually better marked to the right of the sternum than near the apex and may be upright or diphasic. In leads from the right side of the precordium, a Q wave is not normally present, except occasionally to the right of the sternum.[5a] The R wave is small and narrow and the S wave deep and relatively broad. The peak of R occurs early in the QRS interval. In leads from the left side of the precordium, the R wave is tall and relatively wide, often preceded by a Q wave and followed by an S deflection of an amplitude lower than that nearer the sternum. The peak of R is about 0.02 second later in leads from the left side of the precordium than in leads from the right side of the precordium. Between the right side of the precordium, where may be obtained QRS complexes with small R and deep S waves, and the left side of the precordium, which yields tall R and small S waves, there lies a transitional zone yielding complexes of intermediate form. The ventricular complexes of leads from this transitional zone may display notching and other peculiarities of form.

In a normal adult, the maximum upward deflection of the ST interval is 2 mm. Depression of any degree has been described as abnormal by Katz [6] but has been considered as normal by Pardee [5b] up to a maximum of 0.6 mm. The T wave is always upright and large in the region of the apex but may be diphasic or inverted in the region of the sternum in young adults. A well developed U wave is frequently observed.

Children.—A few papers have been published describing the features of precordial electrocardiograms obtained from normal children.[7] The measurements noted in these electrocardiograms have been summarized in table 1.[8]

The only study which included the use of six precordial leads [7e] was made prior to the publication of the recommendations of the Committee on Standardization, and the positions chosen were not identical with the standard positions. In the remaining studies, the precordial electrode was placed to the left of the sternum with the remote electrode either below the left scapula or on the left leg.

In these tracings from children, negative P waves are reported to be relatively common, especially near the sternum.

As in the case of adults, QRS complexes with small R and deep S waves are usually obtained

5. (*a*) Wood, F. C., and Wolferth, C. C.: Recent Developments in Precordial Electrocardiography, Mod. Concept Cardiovasc. Dis., 1939, vol. 8. (*b*) Pardee, H. E. B.: Clinical Aspects of the Electrocardiogram, ed. 4, New York, Paul B. Hoeber, Inc., 1941. (*c*) Wilson, F. N.; Johnston, F. D.; Rosenbaum, F. F.; Erlanger, H; Rossman, C. E.; Hecht, H.; Cotrim, N.; Menezes de Oliveira, R.; Scarsi, R., and Barker, P. S.: The Precordial Electrocardiogram, Am. Heart J. **27**:19, 1944.

6. Katz, L. N.: Electrocardiography, Philadelphia, Lea & Febiger, 1941.

7. (*a*) Rosenblum, J., and Sampson, J. J.: A Study of Lead IV in Children with Especial Reference to the Direction of Excursion of the T Waves, Am. Heart J. **11**:49, 1936. (*b*) Messeloff, C. R., and Pomerantz, A.: A Study of Lead IV in Normal Children and in Ambulatory Children with Cardiac Disease, Am. J. Dis. Child. **53**:1485 (June) 1937. (*c*) Master, A. M.; Dack, S., and Jaffe, H. L.: Chest Leads in Normal Children, Proc. Soc. Exper. Biol. & Med. **32**:1529, 1935. (*d*) Robinow, M.; Katz, L. N., and Bohnung, A.: The Appearance of the T Wave in Lead IV in Normal Children and in Children with Rheumatic Heart Disease, Am. Heart J. **12**:88, 1936. (*e*) Master, A. M.; Dack, S., and Jaffe, H. L.: The Precordial Lead of the Electrocardiogram of Normal Children, Am. J. Dis. Child. **53**:1000 (April) 1937. (*f*) Dwan, P. F., and Shapiro, M. J.: The Four Lead Electrocardiogram of Children, ibid. **54**:256 (Aug.) 1937. (*g*) Groedel, F. M.; Kisch, B., and Reichert, P.: Changes in the Standard Electrocardiogram and Chest Leads During the First Stages of Life, Cardiologia **6**:1, 1942.

8. In referring to previous studies in which the technic described was that originally used by Wolferth and Wood (the lead wires being attached so that polarity of the waves in the precordial leads is the reverse of that in the standard leads), the terminology has been adjusted in the present paper so that all terms are in accordance with the revised technic suggested by the committee on standardization.

from the right side of the precordium, whereas the left side of the precordium yields a reverse picture. This is not invariably so, however, since some normal children may yield QRS complexes from positions near the sternum in which the amplitude of R may be greater than of S. Even in such instances, however, the amplitude of R tends to increase and the amplitude of S to decrease as the apical region is approached. (fig. 1). The presence of triphasic complexes with double upward deflections in tracings from the sternal region of normal children will be commented on later in the course of this paper.

No elevation of the ST interval greater than 2 mm. has been described. Depression ranging from 0.5 to 1 mm. has been observed, especially near the sternum [7e] and in infants.[6]

The most striking variation from the tracing from an adult is in the contour of the T wave, which is usually inverted near the sternum but may not infrequently be inverted in the region of the apex also. The frequency of inverted T waves diminishes with the increased age of the child. At a position 4 cm. to the left of the midsternal line, T was found inverted in 55 per cent of all children aged 2 to 6 years, in 31 per cent

TABLE 1.—*Smmary of Published Data on Precordial Leads of Normal Children* [8]

	Messeloff and Pomerantz [7b]	Robinow, Katz and Bohnung [7d]	Master, Dack and Jaffe [7e]		
Number of children	20	61	71		
Age in years	?	<1 to 16	2 to 15		
Position of chest	C_3	C_3	2 Cm. Left of Midsternal Line	4 to 6 Cm. Left of Midsternal Line	8 Cm. Left of Midsternal Line
Position of remote electrode	Posterior chest	Left leg	Left leg	Left leg	Left leg
Limits of amplitude (millimeters)					
P	1 to 2	1.5 to −2.0	1 to −1	1 to −1	0.05 to −1
Q	.....	.....	.....	.....	0.5 to 2
R	3 to 18	1 to 19	1 to 22	1 to 30	1 to 33
S	.....	3 to 40	2 to 30	0.5 to 40	0 to 17
Total QRS	5 to 38	7 to 57			
ST deviation	.....	0.0 to +2	−1 to +1	1 to −1	0.5 to −1
T	1.5 to 4	6.5 to −5	3 to −8	4 to −6	5 to −1
Duration (seconds)					
P	0.04 to 0.08			0.02 to 0.06	
PR	0.10 to 0.16			0.06 to 0.18	
QRS	0.05 to 0.08			0.06 to 0.09	

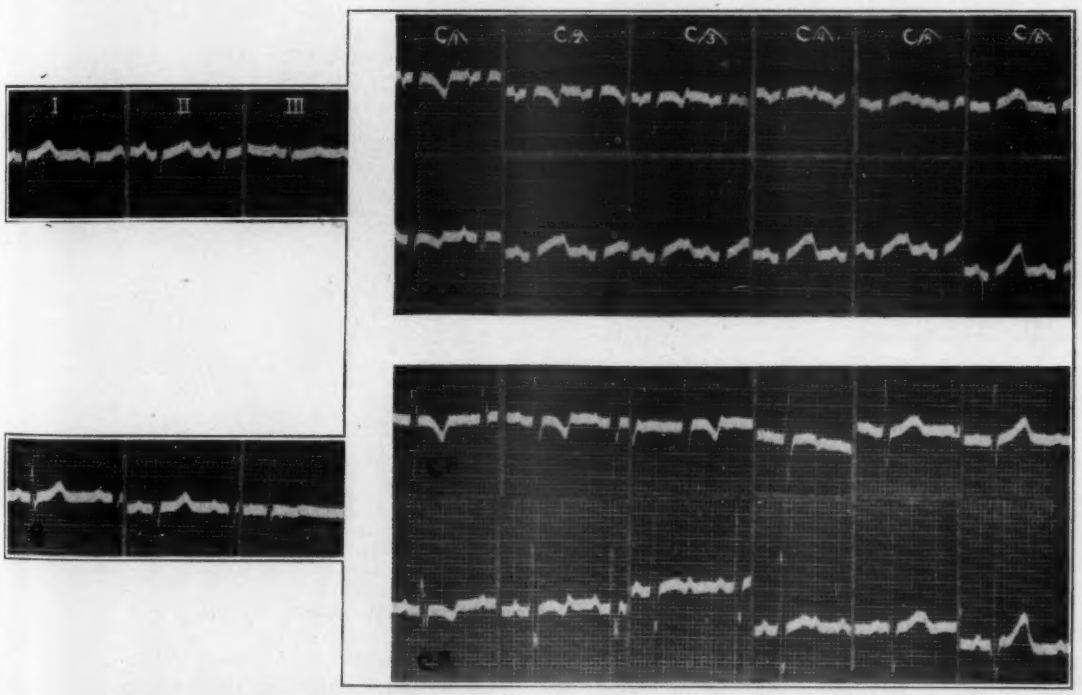

Fig. 1.—Comparison of CF and CR leads from 2 children with normal hearts who presented triphasic QRS complexes in the CF_1 lead: *A*, a 5 year old girl, and *B*, a 7 year old boy. The CR_1 lead in each instance presents not only double upward deflections but also double downward deflections. Note the smaller degree of inversion of T waves in the CR leads as compared with the CF leads.

of those aged 7 to 10 years and in 5 per cent of those aged between 11 and 15 years.[7e] In no series has an amplitude of an inverted T wave greater than 8 mm. or an upright T wave greater than 6.5 mm. been reported.

Depending on the age of the child and the position of the electrode on the chest wall, negative, diphasic or positive T waves may therefore be normal in childhood. The degree of inversion is greatest in the region of the sternum. Notching is frequently seen, representing one phase as the T wave passes progressively from an inverted through a diphasic to an upright configuration, at first with a broad, notched or double-peaked summit and finally with an angulated apex (fig. 1). Not only may the contour of the T wave vary considerably in the same child at different points on the precordium, but pronounced variations in contour at the same precordial position may also be noted in tracings taken a few months apart. Variations in contour of T waves, therefore, may be considered of significance only if they occur in rapid sequence and only if consecutive tracings have been obtained from identical points.

TABLE 2.—*Summary of Electrocardiographic Data for 150 Patients from the Children's Hospital*

Diagnosis	Patients, Number	L.L.N.* P.L.N.	L.L.N. P.L.A.	L.L.N. P.L.A.(?)†	L.L.A. P.L.N.	L.L.A. P.L.A.	L.L.A. P.L.A.(?)†
Rheumatism, active; potential heart disease	14	10	3	1	0	0	0
Rheumatism, active, with carditis	17	9	2	0	1	5	0
Rheumatism, inactive; potential heart disease	13	12	1	0	0	0	0
Rheumatism, inactive; chronic endocarditis	19	12	1	1	2	3	0
Rheumatism, total	63	43	7	2	3	8	0
Nephritis‡	20	10	1	0	5	4	0
Miscellaneous infections other than above	15	13	0	0	1	0	1
Miscellaneous illnesses of noninfectious origin	11	6	1	0	2	2	0
Congenital cardiac anomalies	26	12	0	4	3	7	0
Normal children	16	14	0	2	0	0	0
Total	151§	98	9	8	14	21	1

* Abbreviations: L.L., limb leads; P.L., precordial leads; N, normal; A, abnormal.
† Triphasic QRS complex was present in a single tracing; no further electrocardiograms were taken.
‡ Includes 16 cases of acute glomerulonephritis, 1 of acute pyelonephritis and 4 of chronic nephritis.
§ One child was admitted twice.

TABLE 3.—*Summary of Abnormalities in Leads CF_2 and CF_4*

Diagnosis	Patients, Number*	ST Deviation	P	Abnormal QRS‡	Abnormal QRS?†	Absent R	Large T	Positive T
		Lead CF_2						
Rheumatism	13	0	6	4	2	4	1	0
Nephritis	4	1	1	2	0	0	0	0
Miscellaneous infections	0	0	0	0	1	0	0	0
Noninfectious conditions	3	0	1	0	0	0	0	2
Congenital cardiac anomalies	7	0	2	4	4	0	0	2
Normal	0	0	0	0	2	0	0	0
Total	27	1	10	10	9	4	1	4
		Lead CF_4						
Rheumatism	6	1	1	1	0	2	2	
Nephritis	1	1	0	0	0	0	0	
Miscellaneous infections	0	0	0	0	0	0	0	
Noninfectious conditions	1	0	1	0	0	0	0	
Congenital cardiac abnormalities	1	0	1	0	0	0	0	
Normal	0	0	0	0	0	0	0	
Total	9	2	3	1	0	2	2	

* Exclusive of persons with questionable abnormal QRS complexes.
† Triphasic QRS complex present in a single tracing; no further electrocardiograms taken.
‡ Triphasic or splintered QRS complexes.

P Wave.—An amplitude greater than 2 mm. in lead CF_2 or 1 mm. in lead CF_4, whether upright, diphasic or inverted, or a duration greater than 0.08 second was considered abnormal (tables 2 and 3). Simple notching in itself was not deemed significant. Such abnormalities were noted in the tracings of 10 persons, all associated with similar changes in the limb leads. In only 2 instances were variations more striking in the precordial leads than in the limb leads. In all 10 instances, abnormal P waves were noted in the CF_2 lead; in only 3 cases were they present in the CF_4 lead also (table 3).

QRS Deflection.—The presence of a Q wave in the CF_2 lead is considered abnormal. No such Q wave was noted in the present series. In previous reports on precordial electrocardiograms from normal children, no Q wave of amplitude greater than 3 mm. had been noted in

the apical region. Six children in the present series yielded Q waves in the CF_4 lead with amplitude greater than this (range 4 to 6.5 mm.). In all instances, the Q wave was less than 25 per cent of the associated R wave. One of these tracings (with a Q wave of 4 mm.) was obtained from a normal child with a juvenile functional systolic murmur, because of which she had been referred for study. Because of the high amplitude of the associated R waves, it was decided that none of these Q waves could be considered abnormal.

An absent R wave or one smaller than 1 mm. in either lead was considered abnormal. Such small or absent R waves were observed in 4 children, all with rheumatic infection (fig. 2). Two were noted in the CF_2 lead only and two in both precordial leads. The limb leads were normal in 3 children. Two of the latter children showed no clinical evidence of cardiac involvement.

Triphasic Complexes.—Triphasic complexes (double upward deflection; M-shaped QRS complex) have been described as always abnormal in leads CF_2 and CF_4[6] and as having the same significance of the presence of myocardial disease as absence of an initial deflection.[2d] Such triphasic complexes were noted in the CF_2 leads of 15 children in the present series. Two, however, presented no evidence of heart disease or of an infectious state at the time the tracing was

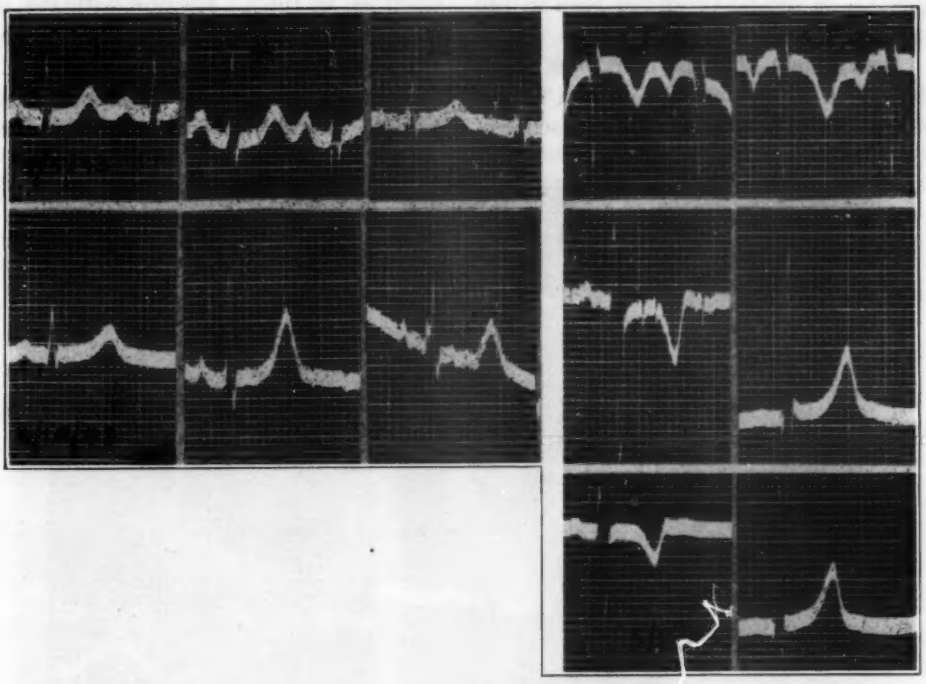

Fig. 2.—Abnormal precordial leads from an 8 year old boy with active rheumatic infection who presented no clinical signs of cardiac involvement. April 5, 1943: R, absent; R′, small; P, negative, slightly deeper than normal, and T, inverted in each precordial lead. April 10, 1943: (standardization incorrect; 1.2 cm. instead of 1 cm.) P now upright, R of normal amplitude, T upright in CF_4. Limb leads normal with top normal PR (0.16).

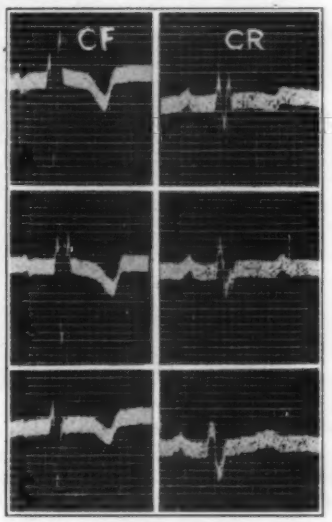

Fig. 3.—Comparison of CF and CR leads from an 11 year old boy with normal heart who presented a triphasic QRS complex in the CF_1 lead. Precordial electrode placed in (*A*) the third interspace at the right margin of the sternum, (*B*) the fourth interspace and (*C*) the fifth interspace. Distortion of QRS complexes is still present in the CR leads. Note that T waves are more nearly normal in the CR leads than in the CF leads.

taken. One child, referred because of a history of hemorrhagic nephritis three years previously, had made a complete recovery from his nephritis and presented no clinical evidence of cardiac abnormality. The second child had been in bed two months previously with a febrile illness associated with cough, diagnosed by one physician as due to virus pneumonia and by a second physician as rheumatic because of the presence of seemingly normal hearts. Such complexes have been present more frequently in CF_1 leads than in CF_2 leads.

Messeloff and Pomerantz,[7b] using a precordial electrode in the C_2 position with the indifferent electrode placed posteriorly to the left of the spine (CB_2 lead), reported a 5 per cent incidence of triphasic complexes in 20 children without cardiac disease who were in the hospital for

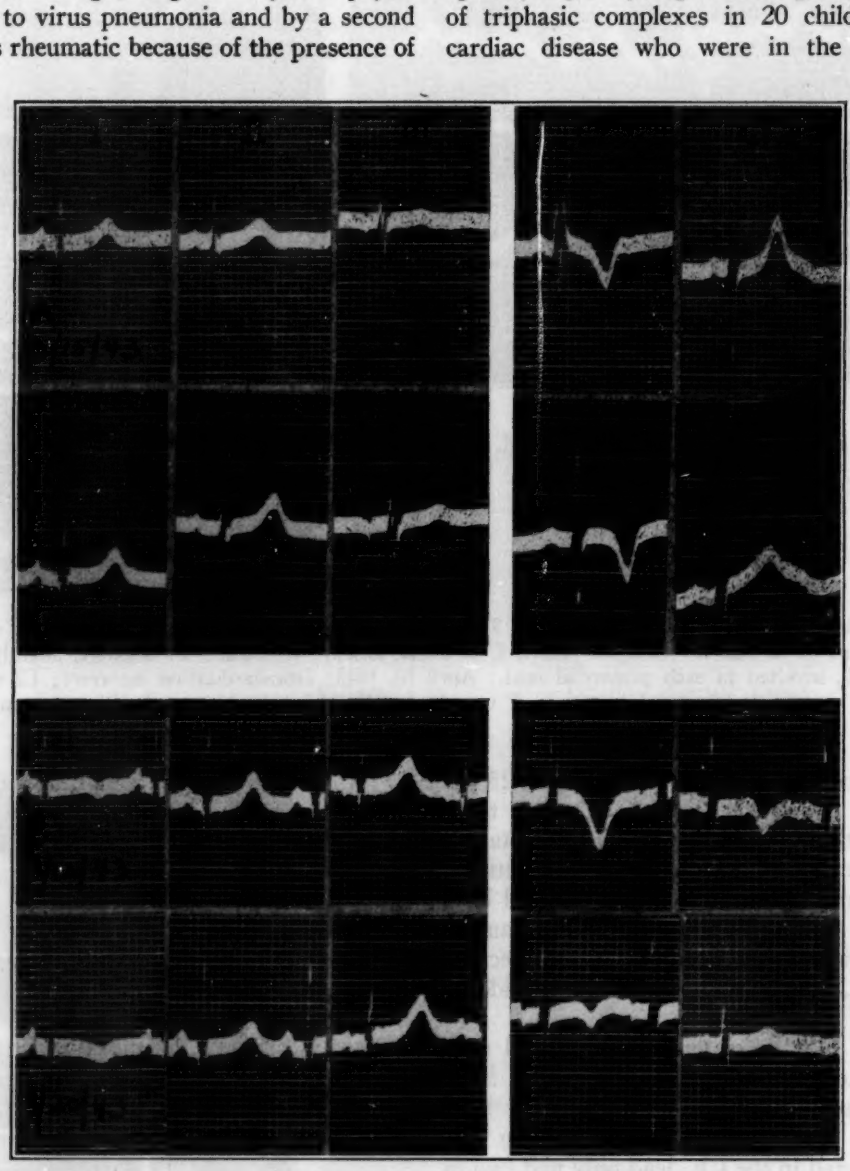

Fig. 4.—Electrocardiograms from 2 children with acute hemorrhagic nephritis presenting a transient triphasic QRS complex in the CF_2 lead. *A*, a 7 year old boy with an onset of nephritis, Feb. 10, 1943; maximum blood pressure 140 systolic and 106 diastolic, heart normal clinically and limb leads normal. *B*, a 5 year old boy with an onset of nephritis, March 3, 1943; maximum blood pressure 140 systolic and 98 diastolic, cardiac gallop rhythm, enlarged liver and inversion of T waves in lead I.

a transient systolic murmur. At the time the electrocardiogram was taken, the child was well, with normal sedimentation rate and no clinical or roentgenologic evidence of cardiac disease. Recently, similar triphasic complexes have been noted in the tracings of 4 other children with treatment of various orthopedic conditions. Rosenblum and Sampson,[7a] also placing the remote electrode on the posterior wall of the chest, reported the presence of triphasic complexes in 12 out of 50 normal children between the ages of 1 month and 16 years. Their pre-

cordial electrode, however, covered the left second, third and fourth sternocostal junctions. Tracings taken from positions as high as the second and third interspaces in normal persons may show distortions of the QRS complex that are not present in tracings taken from the fourth and fifth interspaces.

Since the region to the left of the sternum may yield triphasic complexes in normal children, such complexes were considered abnormal in only 6 children in whom the transient nature of the distortion seemed proved by the presence of only diphasic complexes in subsequent tracings. These subsequent tracings were taken with the electrodes placed to the left of the sternum in the third, fourth and fifth interspaces respectively so as to eliminate the possibility that previous tracings had been obtained erroneously from an interspace other than the fourth. Of the 6 children with transient triphasic QRS complexes, 4 were suffering from rheumatic infection and 2 from hemorrhagic nephritis (fig. 4). (In an additional child with rheumatic infection such complexes were obtained in the second tracing of a series [fig. 5].) The associated limb leads were normal in the tracings of 4 children, 3 with rheumatic infection and 1 with hemorrhagic nephritis. Two of the rheumatic children presented no clinical signs of cardiac involvement.

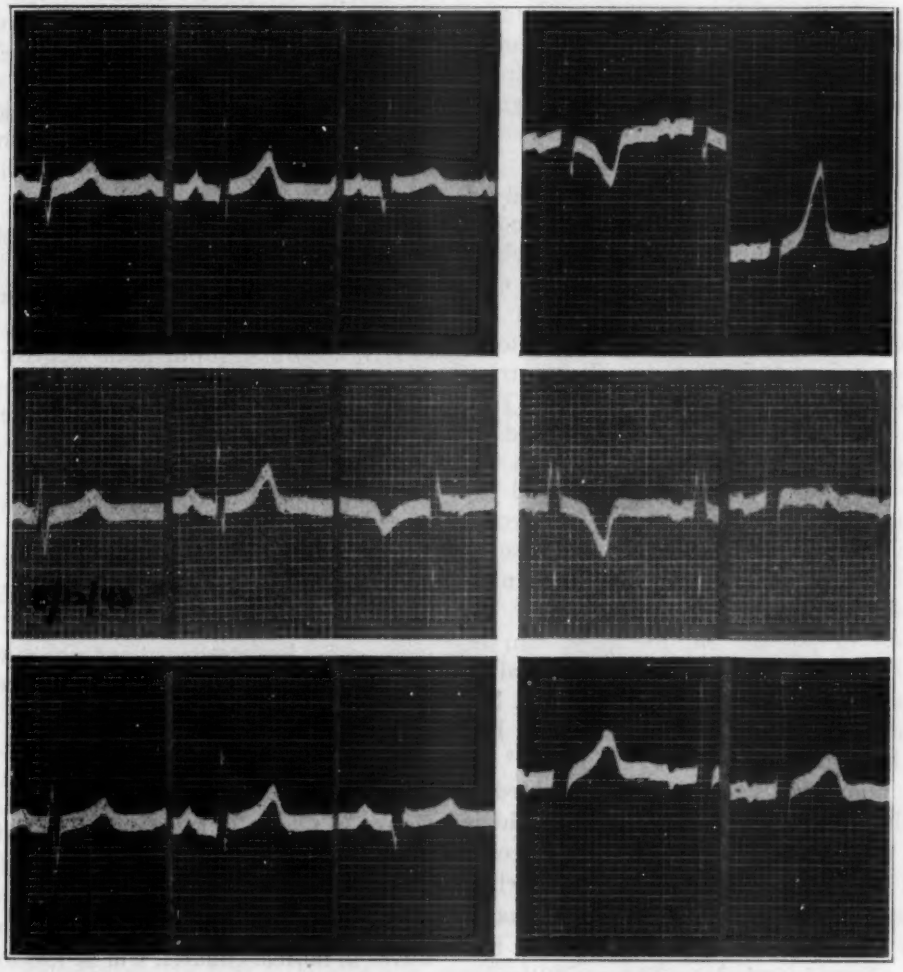

Fig. 5.—Electrocardiograms from a 12 year old boy with active rheumatic carditis. Limb leads were normal. July 3, 1943; diphasic QRS in CF_2 with notching of S near the base line; high-peaked T in CF_4. Aug. 12, 1943: (the tracing in lead III has been incorrectly mounted so that all complexes are reversed) double upward deflection in CF_2 and polyphasic T wave of low amplitude in CF_4. April 7, 1945: (the boy is now 14 years old) rheumatism inactive, single upward deflection in CF_2 and upright T in both precordial leads.

In 9 children from whom only a single tracing had been obtained the abnormal nature of the triphasic QRS complexes present in the CF_2 lead was considered unproved. These include the 2 normal children previously described, 1 child with virus pneumonia, 4 children with congenital cardiac anomalies and 2 with rheumatic infection.

In precordial leads paired with an electrode on one extremity, the potential variations of the precordium are distorted by the potential variations of the limb electrode. It has been suggested by Wolferth[9] that the production of triphasic QRS complexes in precordial leads from normal children may be the result of the magnitude of the variations of potential in the limbs of children, which frequently are especially high in the left leg. Q and S waves tend to be prominent in the limb leads of the child. Since variations of potential from the left leg are subtracted from the variations of potential transmitted to the precordial electrode from the underlying cardiac surface, distortion due to prominent Q or S waves in the left leg electrocardiogram may thus result in double upward deflections in the precordial lead.

This theory would seem to be supported by the fact that the six children who have come under observation with normal hearts which yielded triphasic QRS complexes in CF_1 or CF_2 leads all presented prominent S waves in the limb leads (amplitude ranging from 2.5 to 4 mm. with an average of 3.9 mm.). In the tracings from the 6 children with transient QRS complexes assumed to be abnormal, S and Q waves were of relatively small amplitude in the limb leads (1 mm. or less in 4 children and 1.5 to 2 mm. in 2). Whether a triphasic QRS complex in the precordial lead of a child who presents minimal S and Q waves in the limb leads may be assumed to be abnormal is problematic.

Variations of potential in the right arm of all persons whose limb leads present normal T wave patterns are lower than those in the left leg.[10] The use of CR leads in childhood has therefore been recommended by Wolferth[9] in order to minimize distortion in the precordial electrocardiogram which might be due to high variations of potential in the left leg. A comparison of CF and CR leads in 3 normal children whose CF_1 lead had yielded triphasic complexes showed distortion still present in the CR leads (figs. 1 and 3). These CR leads, however, presented P waves and T waves of greater amplitude when upright and of lower amplitude when inverted than did the CF leads. The fact that the precordial electrocardiogram will reflect most nearly the variations of potential transmitted to the precordial electrode when this electrode is paired with one from the point of lowest potential has been pointed out by Wolferth and Wood.[10]

Pronounced splintering of R or S waves was considered abnormal, as was a duration of QRS greater than 0.09 second. Such splintering was noted in the CF_2 lead of 4 children with congenital cardiac anomalies, associated in 2 instances with prolongation of QRS to 0.10 second. The QRS complexes in the limb leads all showed some abnormality. Complexes in the CF_4 lead were normal or showed slurring or notching of the R or S wave (fig. 6).

Deviation of ST.—A deviation greater than 2 mm. above or 1 mm. below the isoelectric line was considered abnormal. No elevation of ST of this degree was noted. Depression of ST was present in the tracings of 2 children (1 with active rheumatic carditis and 1 with chronic nephritis).

T Wave.—Amplitude of an upright T wave greater than 8 mm. in the CF_2 or CF_4 leads or of an inverted T wave greater than 8 mm. in the CF_2 lead or 6 mm. in the CF_4 lead was considered abnormal. Amplitude as great as 8 mm. in the CF_2 lead has not previously been reported, but an upright T wave of this magnitude was found in the tracing of a normal 10 year old girl in the present series. Only 2 children, both with rheumatic infection, yielded T waves with amplitude that exceeded these limits.

It is to be noted that if CR leads are to be used in preference to CF leads in childhood the normal limits of amplitude of P and T waves will need to be determined in the CR leads. The few measurements on precordial electrocardiograms in childhood hitherto reported have been based on the use of CF or CB leads, the most frequent determinations having been made in the C_2 position. In average children, T waves in CR leads tend to be of higher amplitude when upright and to show a lesser degree of inversion —i. e., to be more nearly normal than T waves in the CF leads. The incidence of inverted T waves in normal children will be less in CR leads than in CF leads (figs 1 and 3).

Not a sufficient number of analyses of precordial leads from normal infants and children have been reported to enable one to decide at what age the presence of an upright T wave in tracings from the region of the sternum may be considered abnormal. No such waves have been reported for normal children under the age of 12, but the total number of observations has been small. In the present series, upright T waves in the CF_2 lead were obtained from 11 children aged 10 to 14 years inclusive and from 4 children aged 7 to 9 years. Two (aged 9 and

9. Wolferth, C. C.: Personal communication to the author.

10. Wolferth, C. C., and Wood, F. C.: The Production of Differences Between Precordial Leads CR, CL and CF, Based on Limb Lead Findings, Am. Heart J. **20**:12, 1940.

10 years respectively) presented normal hearts and were suffering from no infection. Five (aged 7 to 13 years) were children with inactive rheumatic infection and no clinical evidence of cardiac damage. The remaining 8 children (aged 8 to 14 years) were suffering from organic cardiac damage, either rheumatic or congenital in origin, or from active infection. In all instances upright T waves were also present in the CF_4 lead. It was considered advisable to regard the upright T waves obtained from the sternal region of these older children as normal.

Whether such upright T waves in both leads should be considered normal in 2 girls aged 4 years each and in 2 infants less than 6 months of age seemed less certain. One of the 4 year old youngsters was suffering from a congenital cardiac lesion associated with cyanosis; concordant inverted QRS complexes were present in the limb leads. The second 4 year old child was ill with celiac disease and severe anemia. Of the 2 infants, 1 had a congenital cardiac anomaly with associated severe pulmonary infection; the second, polycystic kidneys with pyelonephritis and hypertension. For the purpose of this analysis, it was decided to consider these T waves abnormal.

Since delayed conduction time and arrhythmia may be observed equally well in standard and in precordial leads, the presence of these findings was ignored.

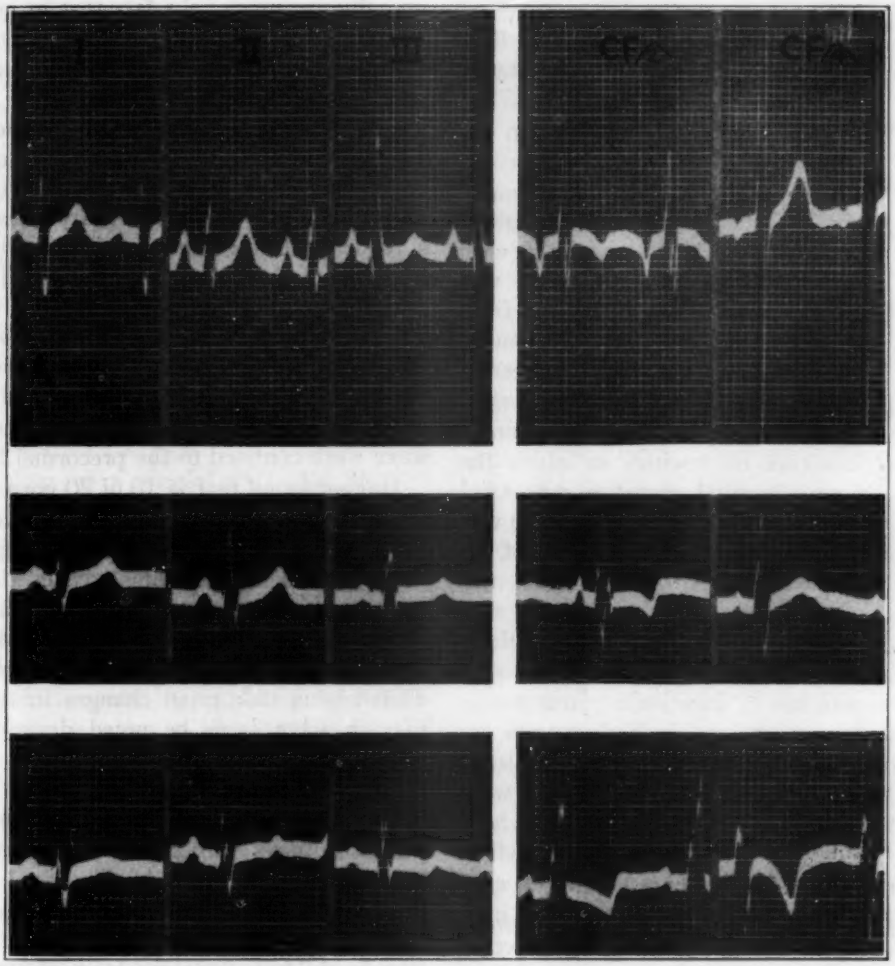

Fig. 6.—Electrocardiograms from 3 children with congenital cardiac anomaly (clinical diagnosis, interatrial septal defect) with abnormal notching of QRS complexes. *A*, a 6 year old girl: S_1 slurred at apex; R_3 notched, and S in CF_2 splintered. *B*, a 14 year old boy: R_1 S_1 and R_3 slurred, R_3 notched, QRS polyphasic in CF_2, and R and S slurred in CF_4. *C*, an 8 year old boy: QRS complexes slurred or notched in all limbs and precordial leads, and QRS triphasic in CF_2.

COMPARISON OF CF_2 AND CF_4 LEADS

Abnormal characteristics were present in the CF_2 lead three times as frequently as in the CF_4 lead (table 3). This was due in large part to the prominence of changes in the P waves and

of abnormal QRS complexes in this lead as compared with the CF_4 lead.

COMPARISON OF LIMB LEADS AND PRECORDIAL LEADS

For 98 children the tracings obtained from both limb and precordial leads were considered to be within normal limits. For 22 children both sets of leads were considered abnormal, including 1 child with a questionably abnormal triphasic QRS complex in the CF_2 lead. For 31 children (20 per cent of the group) there was disagreement between observations in limb and precordial leads. These include 8 children for whom no decision could be reached as to the abnormality of triphasic QRS complexes in the CF_2 lead.

Excluding those tracings with questionably abnormal triphasic QRS complexes, the highest incidence of normal limb leads associated with abnormal precordial leads (11 per cent) was obtained from the 63 children suffering from rheumatic infection. Only one such combination of leads (5 per cent) was noted in the electrocardiogram from the 20 children with nephritis. The nephritic group, on the other hand, produced the highest incidence of tracings in which the limb leads were abnormal and the precordial leads normal (25 per cent). This combination was found in only slightly less than 5 per cent of the rheumatic children. There was no discrepancy in observations among the group of children with congenital cardiac anomalies or among those whose hearts were considered normal, with or without the presence of functional murmurs.

Of particular interest are 3 children with active rheumatic infection and no clinical evidence of cardiac involvement whose limb leads were considered to be within normal limits but whose precordial leads revealed abnormalities which were interpreted as indicating the presence of myocardial damage—absence of R waves in 2 and transient presence of a triphasic QRS complex in 1.

Dwan and Shapiro,[7f] using a single precordial lead (CB_2), found that the fourth lead from 33 children with congenital heart disease added no information to that obtained from standard limb leads. In the case of 72 children with subacute rheumatic heart disease, however, the use of the fourth lead raised the incidence of electrocardiographic changes which could be ascribed to myocardial damage to 36 per cent, as compared with an incidence of 29 per cent in limb leads only. Messeloff and Pomerantz,[7b] also using the CB_2 lead, came to the conclusion that the precordial lead supplied no further information concerning ambulant children with heart disease than could be secured from standard leads.

According to Robinow, Katz and Bohnung,[7d] tall and broad P waves, absence of R waves, deviation of ST (more than 2 cm. above or any extent below the isoelectric line), prolonged span, pronounced notching and triphasic appearance of QRS were the only signs of disease of the heart to be obtained in a single CF_2 lead from a rheumatic child. In contrast with the adults, the contour of the T wave in a single record was of no value because of the fact that in normal children negative and diphasic T waves are common. These authors, however, did find a higher incidence of negative, diphasic and polyphasic T waves in the group of rheumatic children, especially in active stages of the disease, than in the normal control group. Serial curves from 24 patients with rheumatic heart disease showed a tendency toward increase in amplitude of R waves as the activity of the rheumatic infection subsided, together with deviation of the ST segment in the acute stage in 4 cases and variation in contour of the T wave in 16 cases during the active stage as compared with the stage of clinical improvement. In 4 cases the changes in the T wave were confined to the precordial lead.

Having found that in 10 of 20 normal children the contour of the T wave in the precordial lead had changed over a period of six to eight months, Robinow and his associates advised the exercise of caution in the interpretation of changes in the T wave in serial electrocardiograms. It has been the experience at the Children's Hospital of Philadelphia that rapid changes in the T wave may in some cases be noted during the early weeks of active rheumatic infection. The diagnostic importance of changes in the T wave in precordial electrocardiograms repeated within a period of days rather than of months should therefore not be ignored. The final conclusion of Robinow and his associates regarding the limitation of the practical value of the precordial lead in children suffering from rheumatic heart disease is probably true so far as children with well marked chronic rheumatic endocarditis or with inactive infection are concerned. In such children only rarely will precordial leads add information that cannot be obtained from the standard limb leads. In a small number of children with active rheumatic infection, however, the precordial leads may yield clues to the presence of myocardial damage that cannot be obtained from the limb leads or from clinical examination.

COMMENT

In comparison with the precordial electrocardiograms of adults, the most striking findings

in those of normal children are the tendency to the presence of negative P waves especially in the region of the sternum and of negative or diphasic T waves in the region of the apex as well as of the sternum. (The incidence of such inverted P and T waves as well as the degree of inversion may be expected to be less in CR leads than in CF leads.) In addition, a small number of normal children will yield from the region of the sternum triple QRS complexes with double upward deflection or diphasic complexes with R waves greater in amplitude than the corresponding S waves.

The presence in tracings from normal children of features which would be interpreted as abnormal in adults necessitates the use of caution in the interpretation of a single electrocardiogram obtained from one or more precordial positions in childhood. Some of the electrocardiograms reported as normal in the present series might have shown themselves to be abnormal, however, if compared with subsequent tracings taken from identical positions within a short period. A few were so proved to be abnormal, but the number of serial tracings was too small to warrant a comparative analysis. The error inherent in the reading of a single precordial electrocardiogram applies also to the interpretation of a single set of limb leads. Although the differences between the limb leads of children and of adults are relatively small as compared with differences between the precordial leads, the limits of normal variation in limb leads are so great that a tracing which must be diagnosed as within normal limits may actually be abnormal for the person concerned. This has been well demonstrated by various authors in serial electrocardiographic studies of patients with acute glomerulonephritis.[11] In an analysis of single tracings, such as the present one, therefore, the incidence of abnormal electrocardiograms must be underestimated.

What diagnostic information can precordial leads contribute? Conduction defects and most arrhythmias are no better demonstrated than in limb leads. In cases of paroxysmal tachycardia or of auricular fibrillation in which P waves cannot be seen clearly in the limb leads, a precordial lead from the right of the sternum may be of aid in determining the site of origin of the cardiac impulse since this region tends to yield prominent P waves. In the present series, abnormal P waves due to enlargement of the auricles, however, were better demonstrated in limb leads than in precordial leads.

Certain conditions in adult life for which precordial leads are most likely to yield information of diagnostic importance rarely present problems in childhood—myocardial infarction, for example, or differentiation between right and left bundle branch block. It is possible that a more exact study of multiple precordial leads in congenital cardiac anomalies may yield a clue to the presence of hypertrophy of the right or left ventricle or both, which, added to information obtained from clinical and roentgenologic examination, might lead to a more exact anatomic diagnosis.

The most important information to be supplied by the electrocardiogram in childhood is that leading to the detection of myocardial disease due to infection. It is to be emphasized that changes in the electrocardiogram which may be so interpreted, whether in limb or precordial leads, are not in themselves specific. Similar variations may reflect the end result of myocardial damage due to etiologic factors of widely differing nature. The possible site of injury may at times be postulated from the electrocardiographic picture. The probable etiologic agent, however, can be determined only on the basis of associated clinical signs. For example, one is not justified in making a diagnosis of rheumatic infection on the basis of a prolonged PR interval alone even though such an electrocardiographic feature occurs not infrequently in association with this disease. In the present series, prolongation of the PR interval was observed in 3 children suffering respectively from a congenital cardiac anomaly, erythroblastic anemia and chronic nephritis. If the clinical picture, however, justifies the diagnosis of rheumatism or of any specific infection, the presence of abnormal or rapidly changing complexes within the standard or precordial electrocardiogram justifies the assumption that myocardial damage exists.

Since rheumatic infection is the most important disease that may attack the heart of childhood, it is of interest that in the present series, as in previous studies,[7d,f] a small group of children with active rheumatic infection showed abnormal changes in the precordial leads that were not present in the limb leads. Three such children in the present series showed no clinical signs of cardiac involvement. The use of precordial leads for children with active rheumatic infection would seem to present an additional clue to the presence of myocardial damage in a small number of cases. In acute glomerulonephritis, on the other hand, electrocardiographic changes

11. Ash, R.; Rubin, M. I., and Rapoport, M.: Electrocardiographic Variations in Acute Glomerulonephritis, Am. J. Dis. Child. **67**:106 (Feb.) 1944.

were seen more frequently in the limb leads than in the precordial leads.

SUMMARY

An analysis of the precordial leads CF_2 and CF_4 (single tracings) taken from 150 children is presented.

The reported differences between the precordial electrocardiogram of the normal child and of the adult are described. In addition, the occasional presence of triphasic QRS complexes with double upward deflection in tracings taken from the sternal region of the normal child is noted.

In the group of children with acute glomerulonephritis there was a greater tendency to the presence of abnormal changes in the limb leads than in the precordial leads.

Abnormal precordial leads associated with normal limb leads were noted with greatest frequency among the children with active rheumatic infection.

There was no discrepancy in the diagnosis of precordial and limb leads from children with congenital cardiac anomalies or with hearts considered to be normal, with or without the presence of juvenile functional murmurs.

5636 Pine Street (43).

TRICHURIASIS IN CHILDREN

A CLINICAL SURVEY OF FIFTY CASES AND REPORTS OF THREE CASES WITH HEAVY INFECTION AND STRIKING CLINICAL SYMPTOMS

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Most patients with trichuriasis show little or no clinical evidence of infection. From time to time, however, authors have recognized that unusually heavy infection may result in severe illness. Swartzwelder [1] reported the cases of 81 patients admitted to Charity Hospital, New Orleans, because of trichuriasis. Craig and Faust [2] have stated that in cases of heavy uncomplicated whipworm infection, the patients show pronounced emaciation, dry skin, mucous diarrhea, rarely with blood, and a reduction in hemoglobin to 40 or 50 per cent. These authors stated that such conditions may suggest severe ancylostomiasis and that patients so parasitized soon succumb to the disease unless the worms are removed. In 1908, Musgrave, Clegg and Polk [3] reported 4 cases of severe trichuriasis in the Philippines. The patients were adults, 1 of whom died. Deaths of 3 children, attributed to trichuriasis, have been reported. One was reported by Jamieson and Lauder [4] in 1910, and 2 were reported in 1917 by da Matta.[5]

SOURCE OF MATERIAL

Fifty cases of unmixed whipworm infection were analyzed in an attempt to find additional information in regard to trichuriasis in children. The patients were admitted to the pediatric wards of Gorgas Hospital during the three year period extending from Jan. 1, 1941 to Jan. 1, 1944. Many cases with most striking symptoms were not included in this review because the presence of other helminths complicated the picture. It was not surprising to find these cases of polyparasitism, because a child who ingested enough embryonated ova of Trichuris trichiura to cause a heavy infection to develop was apt to pick up ova of other helminths, especially those of Ascaris lumbricoides.

CLINICAL CONSIDERATIONS

Location of Dwellings.—Living conditions in the Republic of Panama and the Canal Zone were separated into three types as follows:

1. United States government communities, located in the Canal Zone, characterized by minimal crowding, excellent toilet and sewage disposal facilities, paved streets and landscaped yards. Only 3, or 6 per cent, of the children studied in this survey came from such communities.

2. Principal cities of the Republic of Panama (Colón and Panamá). In the center of these cities, overcrowding among the poor is commonplace, facilities for sewage disposal are adequate, although not used to the fullest extent by an uninformed populace, and streets and alleys are paved. In the outskirts of these cities, however, facilities for sewage disposal are minimal, the streets unpaved and landscaping absent. Twenty-two, or 44 per cent, of the children came from such cities.

3. Rural or semirural communities in the Canal Zone or the Republic of Panama (interior), where population is sparse, living conditions primitive and sanitation conspicuous by its absence, even outhouses being seen infrequently. Exactly half of the patients came from such communities.

Age.—The youngest patient was 12 months of age. Six, or 12 per cent, were from 12 to 19 months of age, 22, or 44 per cent, were from 2 to 6 years of age and the remaining 22, or 44 per cent, were more or less evenly distributed among the ages ranging from 7 to 12 years.

From the Pediatric Section of the Medical Service, Gorgas Hospital, Ancon, Canal Zone.

1. Swartzwelder, J. C.: Clinical Trichocephalus Trichiuris Infection: An Analysis of Eighty-One Cases, Am. J. Trop. Med. **19**:473-481 (Sept.) 1939.
2. Craig, C. F., and Faust, E. C.: Clinical Parasitology, ed. 2, Philadelphia, Lea & Febiger, 1940, p. 243.
3. Musgrave, W. E.; Clegg, M. T., and Polk, M.: Trichocephaliasis, with Report of Four Cases Including One Fatal, Philippine J. Sc. **3**:545-566 (Dec.) 1908.
4. Jamieson, J. G. S., and Lauder, J. M.: Cases of Fatal Trichocephaliasis in a Child, Brit. M. J. **2**:1772, 1910.
5. da Matta, A.: Enterotrichocephalose, Brazil méd., Rio de Janeiro **31**: 141-143, 1917.

Thus 56 per cent were under 7 years of age. In the 81 cases reported by Swartzwelder,[1] only 6 children (7.4 per cent) were under 5 years of age, 27 (33.3 per cent) from 6 to 10 years of age, 29 (35.8 per cent) from 11 to 15 years of age and the remaining 19 patients (23.5 per cent) from 16 to 25 years of age or older.

Sex.—In this series, there were 28 boys and 22 girls.

Race.—Only 3, or 6 per cent, of the children were white; 31, or 62 per cent, were Negro, and 16, or 32 per cent, were mestizo.

SYMPTOMATOLOGY

The symptoms were difficult to evaluate because many in this group of 50 patients were admitted to the hospital for treatment of other illness and not because of infection with Trichuris trichiura. However, the illness of 11, or 22 per cent, was diagnosed solely as trichuriasis. The same number (11, or 22 per cent) were admitted because of malaria. This was the most common cause for admission among those with associated unrleated diseases.

Frequency of Symptoms Observed in Trichuriasis in Children

Symptoms	Number of Patients	Per Cent
Abdominal distress or pain	9	18
Diarrhea	7	14
Worms seen by parents	7	14
Blood in stools	5	10
Vomiting	5	10
Failure to gain or lose weight	5	10
Fever	3	6
Anorexia	2	4
Prolapse of rectum	2	4
Constipation	1	2
Geophagy	1	2
Malaise	1	2
Pruritus ani	1	2

In 31, or 62 per cent, of the patients there were no symptoms except those obviously attributable to the coexisting disease. The symptoms due to trichuriasis have been listed in order of frequency in the table. The most common complaint was abdominal pain or distress. However, in only 1 patient was the pain localized in the right lower quadrant of the abdomen, thereby simulating appendicitis. Swartzwelder[1] found that 59 of his 81 patients complained chiefly of abdominal pain, and in 16 the pain was localized in the right lower quadrant. He noted 15 with constipation, 5 with diarrhea and an additional 2 with alternating diarrhea and constipation. Two of his patients had blood in the stools. Only 1 of the present series had constipation, but 7 had diarrhea. Five of these with diarrhea had blood in the stools. Parents stated that worms had been seen in the stools of 7 of the children (14 per cent). Swartzwelder[1] did not mention this as a complaint. Nutrition and development were average except for patients whose infections were exceptionally heavy or whose malnutrition was evidently due to the associated unrelated disease.

Judging from the review of these 50 cases and from our personal experience, we conclude that a typical history of severe trichuriasis in the infant or young child is as follows: (1) diarrhea of from one to three months' duration, the diarrheal stools often becoming blood streaked as the disease progresses; (2) recurring abdominal pain and tenesmus; (3) progressive loss in weight eventuating in (4) repeated prolapse of the rectum. In cases of prolapse, the parents often notice small white worms attached to the prolapsed rectal mucosa.

Ross[6] reported similar symptoms in an adult with an extremely heavy infection. It is felt that these symptoms and complaints are rather typical of severe trichuriasis, especially in a young subject, and that associated parasites, when present, need have little or nothing to do with this symptomatology. Three cases of unmixed Trichuris trichiura infection are reported to illustrate this syndrome. There were no deaths in this group, nor do the records of the 2,133 autopsies on children performed in this hospital in the past forty years show a death from trichuriasis.

LABORATORY DATA

On examination of the blood nothing significant was observed in the leukocyte and differential counts except perhaps a tendency to eosinophilia. Twelve patients (24 per cent) had eosinophilia (5 to 14 per cent eosinophils), but the degree seemed unrelated to the severity of the infection. Generally speaking, these children were not anemic. The hemoglobin content ranged between 60 and 70 per cent and the erythrocyte count from 3,500,000 to 4,000,000, values which compared favorably with those observed in well children in Panama. Otto[7] arrived at similar conclusions from hematologic studies on children in Louisiana. He thought it probable that no eosinophilia resulted from chronic whipworm infection but that it might follow the initial infection.

6. Ross, F.: Chronic Diarrhea Due to Trichocephalus Trichiuris, Lancet **2**:97-98 (July 25) 1942.

7. Otto, G. F.: Blood Studies with Trichuris-Infested and Worm-Free Children in Louisiana, Am. J. Trop. Med. **15**:693-704 (Nov.) 1935.

TREATMENT

No treatment was found entirely satisfactory. The treatments used in this series were as follows: hexylresorcinol crystoids, 31 cases; tetrachloroethylene, 1 case; *leche de higueron,* 3 cases; gentian violet medicinal, 1 case, and hexylresorcinol crystoids combined with retention enemas of a 1:1,000 solution of hexylresorcinol, 3 cases. Five children were treated with two or more of these medications. Many were treated repeatedly. It was apparent that infection could be reduced but not entirely eradicated, especially in those with a large burden of worms. In our hands, a combination of hexylresorcinol crystoids by mouth and hexylresorcinol given as a retention enema was the most effective of the methods tried in reducing the severity of infection. Treatment with either the fresh latex of the wild fig tree (Ficus laurifolia) obtained locally or with the Colombian proprietary preparation *Higueronia* [7a] proved disappointing. Faust [8] and Caldwell and Caldwell [9] found the fresh latex efficacious in the treatment of trichuriasis.

REPORT OF CASES

Case 1.—A 4 year old mestizo boy from an unsanitated area in the Republic of Panama was admitted to the hospital with the complaints of diarrhea and attacks of abdominal pain for fifteen days. There was a history of his eating dirt whenever the opportunity presented itself. The parents reported that the stools were watery and often blood streaked and that frequent prolapse of the rectum occurred with the bowel movements. Small white worms had been noted moving on the prolapsed rectal mucosa. Although vomiting had occurred at the onset of the illness, this had stopped before his admission to the hospital. He had lost much weight and had become so weak that he was unable to walk. He had been treated for worms in another hospital two years and again two months prior to the present admission. On those occasions, his symptoms were similar to those of the present illness.

On physical examination the following conditions were observed: temperature of 99.8 F.; weight of 22 pounds (10 Kg.); extreme emaciation, and inability to stand steadily on his thin, cranelike legs. Proctoscopic examination revealed many small white worms attached to the rectal mucosa. In other areas several small hemorrhages were noted.

Results of laboratory examination were as follows: hemoglobin content, 60 per cent (Tallqvist); erythrocyte count, 3,400,000; leukocyte count, 7,500, with neutrophils 71 per cent and lymphocytes 29 per cent, and blood smears for malaria, negative. Tuberculin, Wassermann and Kahn tests elicited negative reactions, and repeated cultures were negative for pathogens. Roentgenologic examination of the chest showed nothing of significance. No amebas were found in the stools, and ova of Enterobius vermicularis were not collected by means of swabs with cellophane points. Stools were repeatedly positive for ova of Trichuris trichiura but negative for other parasites or ova.

Course.—The patient had tenesmus and passed frequent small loose stools, consisting principally of mucus streaked with fresh blood. Noticeable prolapse of the rectum occurred frequently with these bowel movements, and on close examination of the prolapsed rectal mucosa eight to ten whipworms were found, their necks sewn through small segments of the superficial mucosa like basting threads. These worms were removed intact with some difficulty, leaving small bleeding points in the rectal mucosa. They were identified as Trichuris trichiura.

At first the patient was unable to tolerate food of any kind. Food passed through the gastrointestinal tract almost unchanged. For some time, attempts to increase the simplest diet resulted in a flare-up of vomiting and diarrhea. He was treated with seven courses of hexylresorcinol by mouth, four of which were followed by retention enemas of a 1:1,000 solution of hexylresorcinol. He was also given enteric-coated tablets of gentian violet medicinal for fourteen days. Although diarrhea persisted, the child began to gain in weight slowly, and finally it was possible to increase the diet gradually until it was adequate. The stools remained positive for ova of Trichuris trichiura, but the infection apparently had been reduced by repeated treatment to the point that he was able to tolerate ordinary diet with no more diarrhea or prolapse of the rectum. The child gained 9 pounds (4.1 Kg.) during his ten week stay in the hospital.

Case 2.—A 13 months old mestizo girl from an unsanitated area in the Republic of Panama was admitted to the hospital because of fresh lye burns on the lips and mouth. For about a month this girl had had severe diarrhea, the stools being described as small and containing blood and mucus. She cried with pain at each bowel movement. Her appetite had become poor, and she had lost much weight. Prolapse of the rectum had been noted twice. The past history was noncontributory.

Physical examination revealed a weight of 17 pounds (7.7 Kg.), poor nutrition, severe dehydration and chemical burns on the lips and anterior portion of the mouth. There was no evidence of burns extending beyond the anterior pillars.

Laboratory examinations showed: hemoglobin content, 70 per cent (Tallqvist); erythrocytes, 4,200,000; leukocytes, 8,400, with the differential count within normal limits; blood smears for malaria, negative; reactions to Wassermann and Kahn tests, negative, and cultures of stools, negative for pathogens. Ova of Enterobius vermicularis were not obtained with a cellophane swab. Stools were repeatedly positive for ova of Trichuris trichiura but negative for other ova or parasites.

Course.—The patient had a persistent diarrhea, the stools containing bright red blood. A low grade fever (temperature up to 101 F.) was present, but nothing was found to account for this fever except trichuriasis. She received four treatments of hexylresorcinol and

7a. This preparation is the latex of the wild fig tree with a preservative, probably sodium tartrate.

8. Faust, E. C.: Personal communication to one of the authors (J. F. M.).

9. Caldwell, F. C., and Caldwell, E. L.: A Study of Anthelmintic Efficiency of Higuerolatex in Treatment of Trichuriasis, with Comment as to Its Effectiveness Against Ascaris Infestation, Am. J. Trop. Med. **9**:471-482 (Nov.) 1929.

two of *Higueronia*. Each of these treatments was followed by a transitory exacerbation of the blood-streaked diarrhea. Following therapy, however, her diet was increased rapidly, with no further recurrence of the diarrhea or of blood in the stools. Although she continued to show ova in the stools, she gained weight rapidly and appeared much improved when discharged from the hospital, sixty-six days after admission.

CASE 3.—A 2 year old mestizo girl from an unsanitated area of the Canal Zone was admitted to the hospital with complaints of watery foul stools, gradual loss of weight and increasing weakness extending over a period of three months.

Physical examination revealed a temperature of 102 F., a weight of 14 pounds (6.4 Kg.) and extreme malnutrition, dehydration, weakness and irritability.

Results of laboratory examinations were as follows: hemoglobin content, 65 per cent (Tallqvist); erythrocytes, 3,700,000; leukocytes, 13,500, with neutrophils, 54 per cent and lymphocytes, 46 per cent; blood smears for malaria, negative, and reactions to Wassermann and Kahn tests, negative. On repeated cultures the stools were free of pathogens, and tuberculin tests elicited negative reactions. The stools were persistently positive for ova of Trichuris trichiura but negative for other ova or parasites.

Course.—The fever present on admission disappeared soon after hydration with parenterally administered fluids. Stools were frequent and watery, despite the fact that the patient received little by mouth except milk. When other food was ingested, the diarrhea became worse. The rectum prolapsed slightly only once, and no frank blood was observed in the stools, although blood cells were found on microscopic examination. The hemoglobin content dropped to 30 per cent (Sahli) and the erythrocyte count to 2,500,000. The child was given three treatments of hexylresorcinol crystoids, three of *Higueronia* and one of hexylresorcinol crystoids followed by a retention enema of a 1:1,000 solution of hexylresorcinol. It was finally possible to give the patient a full high vitamin diet and iron and ammonium citrates. She continued to have five or six large watery stools daily up to the time of discharge, but the anemia was overcome gradually and satisfactory gain in weight was started. When the child was discharged from the hospital five months after admission her weight was up to 23 pounds (10.4 Kg.) and she seemed well. However, the stools were still positive for ova of Trichuris trichiura.

COMMENT

That 22, or 44 per cent, of the patients in this series named the larger cities in the Republic of Panama as their residence seemed contrary to expectation. The figure obviously is misleading, because trichuriasis is not a disease of the city with sanitary facilities. It was felt, however, that many of these children acquired their infections in the country, but were brought to the city later by relatives who worked for agencies of the United States government. Living in the country in Panama literally means living next to the soil, with dirt dooryards, often dirt floors in the dwellings and usually no attempt at sewage disposal or sanitation. The prevalence of such living conditions also explains the frequent association of trichuriasis with other helminthic infections, particularly ascariasis and ankylostomiasis.

The manner of attachment of the whipworm was well demonstrated in case 1. Ross [6] removed a whipworm with forceps on sigmoidoscopic examination and found a collar of intestinal mucosa around the neck of the worm. There is a striking resemblance between the symptoms of severe trichuriasis, as observed in this study, and those of amebiasis. However, careful search of many stools failed to show either amebas or other protozoa in any of these patients.

A clinical survey of 50 cases of infection with Trichuris trichiura in children was made.

Symptomatology, blood findings and treatment are discussed.

Three cases are reported to illustrate the manifestations of severe trichuriasis in a child

ISOLATION OF POLIOMYELITIS VIRUS FROM CREEK WATER BY DIRECT TRANSMISSION TO THE COTTON RAT

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DETROIT

An outbreak of poliomyelitis occurred last year in the town of Perrysburg, Ohio. Although the total number of cases was comparatively small, the epidemic would probably have been one of the greatest in history had it developed in the same relative proportions in a larger community. Several patients who became ill lived near a creek at the eastern border of the town (point *2* on the map, fig. 1). The local chief of police stated that children of his relatives and friends had been wading in the creek at a place marked point *3* on the accompanying map and that several of them had had gastrointestinal upsets which preceded the epidemic. The creek, which traveled over a loam bottom studded with rocks, received drainage water from farms.

The experiments reported in this communication were performed in order to determine whether the water in the creek was infected with the virus of poliomyelitis and, if so, whether the virus could be transmitted directly to the cotton rat. Specimens were taken at various places. Specimen 1, obtained from the creek before it entered the town, on Highway 25, about 500 feet (150 meters) outside the city limits, was clear water. There were but few flies about this area. Specimen 2 was taken about 1.1 miles (1.8 kilometers) away from the first point, just outside the town, on East Boundary Street. This water contained an odorless sediment and was not so clear as specimen 1. There were more flies about this area than about the area from which specimen 1 was taken, but they were not numerous. Specimen 3 was taken in the center of the town, about 6 feet (1.8 meters) from Highway 23. There were three outlets draining into the creek at this point. One was a large conduit which carried water from a road ditch, which was covered as far as the edge of town and then continued uncovered along the side of the road. There were two other small outlets which carried water, and in one instance fecal-smelling waste. The specimen was taken about 15 feet (4.5 meters) from the latter outlet. The current of the creek was slow at this time (1944), and in some places the water was stagnant, everywhere it was muddy. Although this specimen smelled of feces, it was free from gross fecal contamination. There were innumerable flies in the neighborhood but no fecal material on the banks of the roadway.

Aided by the Bachman Memorial Fund and by a grant from the National Foundation for Infantile Paralysis, Inc.

From the Department of Contagious Diseases, City Hospital, Cleveland, and the Department of Pediatrics, Western Reserve University (Dr. Toomey and Mr. Takacs), and the Department of Anatomy, Wayne University (Dr. Weaver).

PROCEDURE AND RESULTS

Attempts were made to find virus in all three specimens. Specimens 1 and 2 were treated according to Kramer's method [1] and later concentrated by fanning in a Visking sack. Beginning July 6, 1944, six attempts were made to transmit to cotton rats any virus which might be present in either of these two samples. The dose of concentrated water administered to each cotton rat was 0.06 cc. given intranasally, 0.06 cc. given intracerebrally, 1.5 cc. given subcutaneously and 3 cc. given intraperitoneally. For each rat the intraperitoneal and subcutaneous injections were repeated five times at intervals of from five to eight days. The results were negative.

Specimen 3 was prepared in the same way as specimens 1 and 2 and was injected in similar amounts into 2 cotton rats (rats 1 and 2). They received subcutaneous and intraperitoneal injections of the same amounts of concentrated water eight days later. The rats died twenty-three and forty-one days respectively after receiving the first injections. Neither animal had

1. Kramer, S. D.; Sobel, A. E.; Grossman, L. H., and Hoskwith, B.: Survival of the Virus of Poliomyelitis in the Oral and Nasal Secretion of Convalescents, J. Exper. Med. **64**:173 (Aug.) 1936.

paralysis. They merely became furred, gradually weakened and died.

A 10 per cent suspension was made up from the cord and the midbrain of rat 1 and injected into 2 other cotton rats. The doses were 0.06 cc. given intracerebrally, 0.06 cc. given intranasally, 0.5 cc. given subcutaneously and 1 cc. given intraperitoneally. In all succeeding attempts at transfer we employed the same doses, of 10 per cent suspensions of the cord and midbrain.

with the cord and the midbrain of a rat fro the second group (rat 3), 4 rats being protecte and 4 being given only virus. When neutralizatio tests were made, the cord and the midbrain we prepared in a 20 per cent suspension and co bined with an equal amount of antipoliomyeli horse serum,[2] so that the final dilution of t suspension of cord and midbrain was alwa 10 per cent. Three of the rats of the gro which received the virus–horse serum mixtu

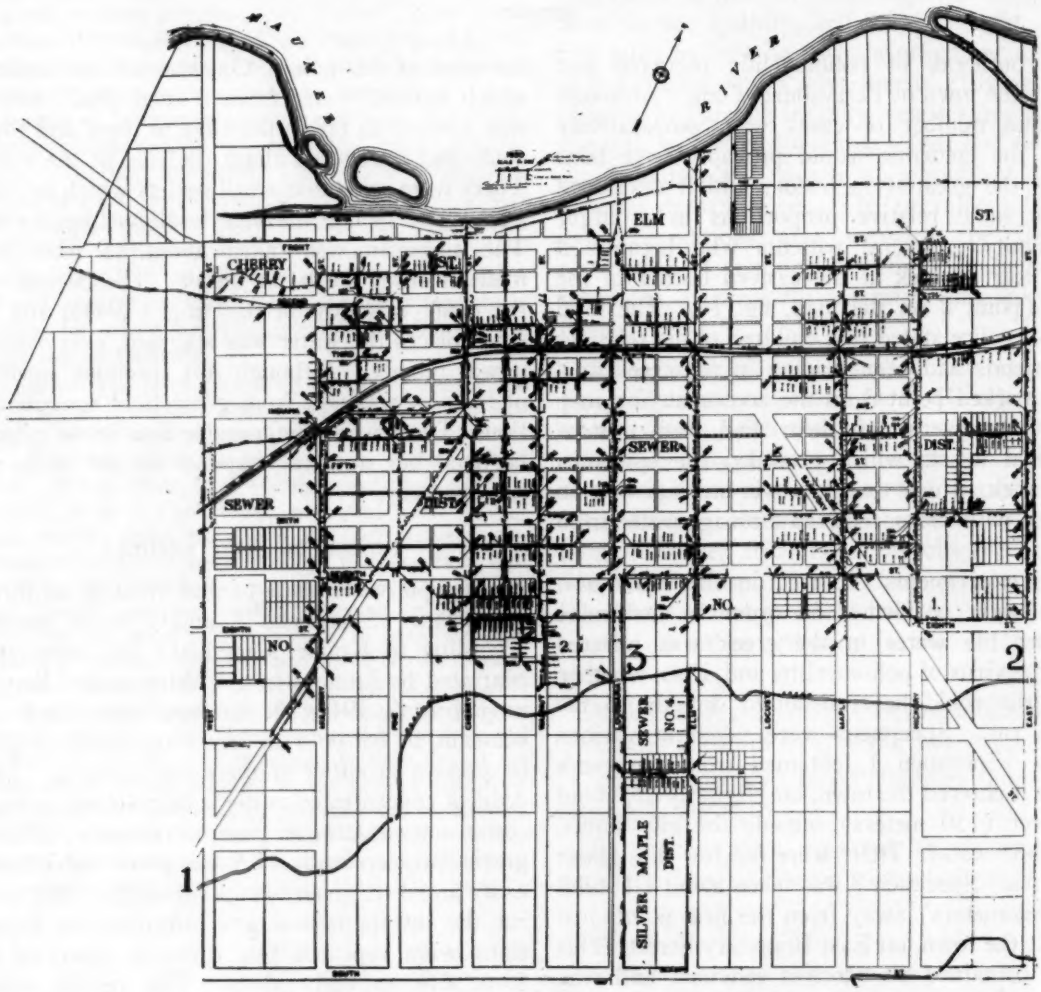

Fig. 1.—Map of Perrysburg, Ohio, showing sewage system.

The rats of the second group (with injections from rat 1) died in twenty-six and thirty-nine days respectively without showing evidence of paralysis. A collateral injection (from rat 2) from the first into a second group of cotton rats, killed 2 rats. One animal died on the eighth and the other on the fourteenth day; neither had paralysis. (See figure 2 for details.)

At this point it was not known whether it would be fruitful to continue the experiment, since none of the animals had become paralyzed. A probing neutralizing experiment was done

lived. The fourth became furred and died the twelfth day. One of the 4 control rats rece ing only virus was killed by one of its grou It had been observed previously and found be weak. One rat died on the eleventh day wi questionable paralysis and 1 on the twelfth d without paralysis, or at the most with que

2. Toomey, J. A.: Poliomyelitis Antiserum Obtain from Horses, Am. J. Dis. Child. **53**:1492 (June) 193 Poliomyelitis Antiserum Obtained from Horses: Neutralizing Effect Against Various Strains of Vir ibid. **55**:1261 (June) 1938.

ionable paralysis. At best there was only a suggestion of protection, but it encouraged us to proceed.

Suspensions from rats of group 2 (rats 4, 5, 9 and 10) were injected into 4 cotton rats of the third group. All 4 animals died—1 on the fourth and 2 on the sixth day, and 1 died of phenomena were due to paralysis. It should be noted that in this experiment the interval of time between injection and death was shorter than in the preceding experiments.

A pooled suspension of cord and midbrain from animals of group 3 (rats 18, 19 and 20) was injected into 4 cotton rats of group 4. Two

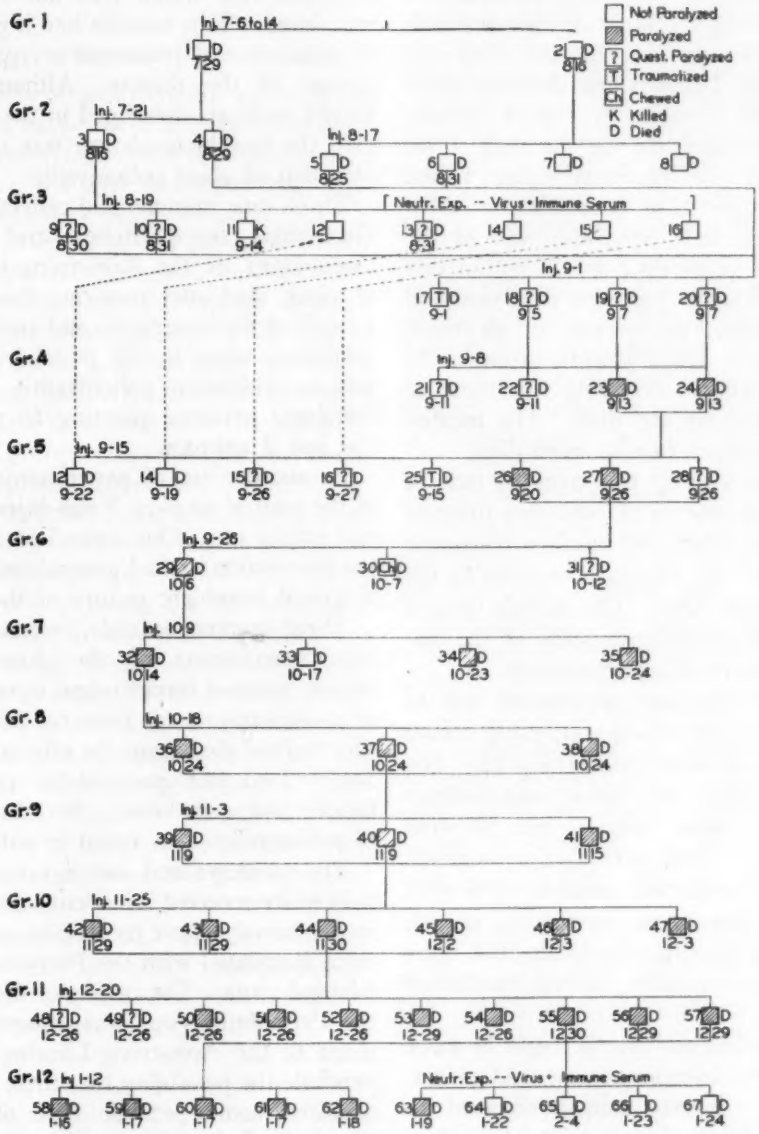

Fig. 2.—Diagram representing injections of concentrated creek water into cotton rats.

perative trauma. Weakness was present in rats, and there was questionable paralysis of e eyelids and toes of 1 (rat 20). Its eyes ared and were glassy, and the toes of the fore- et did not respond to stimulation. Movement the legs was still possible, however, after imulation. In some of the animals observed ter drooling of the tongue and dyspnea were served, but we could not be certain that these died three days later and 2 five days later. The first 2 rats were merely weak; the other 2 were obviously paralyzed in the hindquarters. This was the first time that paralysis was obvious.

A pooled suspension from the paralyzed rats of group 4 was injected into 4 cotton rats of the fifth group. This inoculum was also injected into the rats of group 3 which survived the neutralization experiment. Of the rats of group 5,

1 died of trauma, 2 had paralysis on the fifth and the eleventh day respectively and 1 had questionable paralysis on the eleventh day. Of the rats in group 3 which survived the neutralization experiment 2 had questionable paralysis, whereas the remaining 2 showed no abnormalities.

Material from the fifth group was passed into the 3 cotton rats of the sixth group. One became paralyzed on the tenth day, and 2 died—1 on the eleventh and the other on the sixteenth day, without paralysis. A transfer from the cord of the paralyzed animal (rat 29) was made into 4 cotton rats of group 7. All 4 animals died, 1 becoming paralyzed on the fifth, 1 on the fourteenth and 1 on the fifteenth day; 1 died on the eighth day, without paralysis.

A transfer was made from the cord of the paralyzed animals of group 7 into 3 cotton rats of group 8. All 3 animals became paralyzed and died after an incubation period of six days. From this group to the thirteenth group to be inoculated every animal receiving injections of the virus had paralysis and died. The incubation period ranged from four to seven days.

In an effort to identify the virus as that of poliomyelitis, a suspension of cord was injected into 2 old monkeys which had acquired resistance to the Flexner M. V. strain, as well as to the Trask S. K. strain of virus. The animals became ill and had all the preliminary signs of the disease, but both recovered spontaneously.

The purpose of the next experiment was to repeat the neutralizing experiment, using cotton rats and material obtained from group 12. Ten animals were protected with horse antipoliomyelitis serum in the usual fashion, and 10 were given only virus. All 10 of the controls and 4 of the 10 protected animals died with paralysis within the usual incubation period. The remaining 6 also died eventually, but there was a definite prolongation of the incubation time.

It was thought that our results might be more clearcut if the test injections were made intraperitoneally only. Twenty animals received injections, one-half being given a mixture of virus and saline solution and the other a virus-serum mixture. All the animals withstood the injection. The only fact demonstrated was that poliomyelitis did not develop in the cotton rats after intraperitoneal injections of the material.

Some of the virus from the rats of group 7 was sent to the department of anatomy at Wayne University, Detroit, where one of us (H. M. W.) injected the material into a monkey resistant to the Armstrong-Lansing strain of the virus and into 2 normal young adult monkeys which had not received previous injections. The first animal had no symptoms and seemed protected; the last 2 animals became ill, 1 on the fifth and 1 on the seventh day. One (monkey 8) had flaccid paralysis of the forelegs; the other (monkey 9) had generalized paralysis. In both the histologic picture was that of acute poliomyelitis. The virus from monkey 8 was transferred into 3 cotton rats which had not been previously inoculated. Two animals had a generalized type of paralysis and presented a typical microscopic picture of the disease. Although generalized flaccid paralysis developed in the remaining animal, the histologic picture was not unquestionably that of acute poliomyelitis.

Three rats, immune and resistant to three way (intranasal, intraperitoneal and subcutaneous) inoculations of the Armstrong-Lansing strains of virus, died after receiving the injection, 1 as a result of the inoculation and another of extreme weakness, while in the remaining animal there was no evidence of poliomyelitis. There was no histologic evidence pointing to poliomyelitis in the last 2 animals.

In another set of experiments, a suspension of the cord of monkey 9 was injected into 3 normal cotton rats. One animal died as a result of the inoculation; 2 had generalized paralysis with a typical histologic picture of the disease.

Three immune animals, resistant to two three-way inoculations of the Armstrong-Lansing strain, received intracerebral injections of 0.1 cc. of a suspension made from the cord of monkey 9. One animal died from the effects of the inoculation. Two had questionable paralysis of the foreleg and were killed. No histologic evidence of poliomyelitis was found in either.

The monkeys and cotton rats which had not previously received injections had paralysis within a relatively short incubation period after they were inoculated with the Perrysburg cotton rat-adapted virus. The results of the tests in which the Perrysburg virus was injected into rats immune to the Armstrong-Lansing strain did not preclude the possibility that these cotton rats had acquired some peculiar type of poliomyelitis. They all died without paralysis or were killed after questionable symptoms of paralysis, but in none was definite histologic evidence of poliomyelitis demonstrated.

It was felt that the strain isolated probably was one of poliomyelitis virus, for the following reasons: (1) the virus strain killed all cotton rats after a relatively short incubation period and produced typical paralysis when once the strain was acclimated; (2) the strain was transferable from cotton rats to normal monkeys and produced in them typical experimental poliomyelitis; (3) the

virus was retransferable from the monkey to the cotton rat; (4) recovered animals protected against other strains of poliomyelitis virus when subsequently inoculated did not die with paralysis; (5) the typical histologic picture of poliomyelitis was produced both in cotton rats and in monkeys, and (6) the results of the neutralization tests, although not clearcut, showed a trend in favor of the hypothesis that the virus was a poliomyelitis strain.

COMMENT

The acclimation of poliomyelitis virus to the cotton rat is not easy. In this instance at least four series of transfers were tried before it was certain that our material produced paralysis. Therefore, a virus may be present and still not produce paralysis in the cotton rat even after a few transfer injections. An animal may die without showing any demonstrable evidence of paralysis and yet have virus present in its central nervous system. The acclimation of the strain followed the same definite pattern as in several of our other trials of acclimation. It killed in the first transfer groups, and only after successive transfers did it produce paralysis. Then it became fixed in its reactive power and, finally, after a fairly well fixed incubation period all inoculated animals died with paralysis.

It seems logical to conclude that the virus was probably not present in the drainage from the ground surface water of the surrounding tilled land and that the drainage ditch water itself was of little importance in the spread of the epidemic.

It was curious that although the virus was found at spot 3, it could not be recovered from spot 2, about half a mile (0.8 kilometer) away and in the direction of the flow toward the river. Spot 2 was in the area where the first cases occurred and where one would expect to find the virus if it was present at all. The current was sluggish and the water low at the time the specimens were taken. The sun may have killed the virus as it passed between points 2 and 3.[3]

One would expect to demonstrate the presence of virus in untreated sewage at the height of the epidemic. Its occurrence here might have succeeded rather than have preceded the epidemic and have been of little value from an epidemiologic point of view. However, the continued presence of virus might possibly increase the number of cases, provided exposure could occur. We were not able to isolate virus from the creek as it entered or left the town, but we were successful at a point halfway between. The spot from which it was isolated was near an outlet which may have been used for overflow drainage from septic tanks. The latter may have been inefficient and have allowed virus to pass into the water. That this outlet drained areas where the disease was not found need not disturb one, since it is experience that many persons in a community harbor the virus and yet have no symptoms. In fact, one of us (Toomey) has always believed that the virus is omnipresent in an epidemic area and that finding it in immediate sewage water and in stools would be the rule and not the exception. In this instance its presence would merely demonstrate again that the virus is present in larger numbers of the population than is generally surmised and that the absence of symptoms in persons living in an epidemic area does not signify that the virus is absent from their stools.

In any event, the feces should be efficiently treated before disposal into any open body of water.

CONCLUSION

A strain of virus probably belonging to the poliomyelitis group, was isolated from creek water by direct transmission to the cotton rat.

3395 Scranton Road, Cleveland 9.

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3. Toomey, J. A.: Inactivation of Poliomyelitis Virus by Ultraviolet Irradiation, Am. J. Dis. Child. **53**:1490 (June) 1937. Schultz, E. W.: Recent Advances in the Study of Poliomyelitis, J. Pediat. **1**:358 (Sept.) 1932.

VITAMIN CONTENT OF FIELD-FROZEN KALE

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It is generally agreed that the leafy green vegetables are extremely valuable components of the human diet. These supply vitamins and minerals that are low or lacking in a number of the widely and extensively used food materials, such as flour and sugar. Unfortunately, nearly all the green leafy vegetables are seriously damaged if not destroyed by freezing temperatures. In this locality killing frosts occur relatively early in the season. Gunness [1] found in a fifty year summary of meteorologic records that the average date of the first killing frost was September 21, with extremes of August 22 and October 13. Frequently, following the first killing frost there is a considerable period during which plants that escape the frost thrive. Kale is one of the very few green leafy vegetables grown in this area which survives a killing frost. In fact, ordinarily there is no external evidence that it is at all damaged by the frost. Apparently, in one respect at least, it is improved by freezing, for the pronounced characteristic flavor, which is objectionable to many persons, is greatly reduced and sometimes practically absent after kale has been thoroughly frozen. Because of the scarcity of fresh green leafy vegetables in this area during the late fall after killing frosts have occurred, it seemed desirable to determine the vitamin content of field-frozen kale, i. e., kale which had been subjected to repeated freezing, and this study was conducted for that purpose.

EXPERIMENTAL PROCEDURES

Dwarf Blue-Green Scotch kale (Brassica oleracea acephala), grown in a victory garden, was used for this study. It was planted in early summer and was still growing vigorously when the leaves were picked for assaying. The plants had been set in a row, and the lower leaves overlapped considerably, thus forming a continuous row approximately 18 inches (46 cm.) high and 30 inches (76 cm.) across at the base. The leaves varied in length from 15 to 18 inches (38 to 46 cm.) for the bottom leaves to 2 to 3 inches (5 to 8 cm.) for the small plumelike leaves at the very top of the plants.

The kale was subjected to freezing seven times during the month before any was collected for assaying. The first freezing temperature, 32 F., came October 5. The other freezing temperatures were: 28 F., October 6; 29 F., October 10; 23 F., October 11; 26 F., October 12; 32 F., October 13 and 27 F., November 1. During the interval from October 14 to 31, the minimum daily temperature varied from 38 to 61 F. The minimum daily temperatures while the assays were being made were 34, 34, 37, 32, 38, 38, 31, 31, 30, 34, 28 and 24 F. On a number of mornings when the frozen kale was brought to the laboratory, the leafstalk would break like an icicle, and if the blade of a leaf was struck it would shatter like glass. Yet, when the kale was thawed out slowly at room temperature, the leaves appeared normal, and those that remained on the plants in the field seemed entirely normal after the atmospheric temperature returned to nonfreezing levels. When kale leaves that had been subjected to freezing at 23 F were subsequently picked and cooked, they appeared typical of summer kale except that the pronounced flavor of summer-harvested kale was absent.

Assay Methods.—The kale leaves were picked from the plants in the morning between 8 and 9 o'clock, frozen or not, depending on the atmospheric temperature, and taken directly to the laboratory. If the leaves were frozen, they were allowed to thaw; if not, they were sampled at once. In any case, the coarse midrib was removed, and the blade of the leaves was cut in fine pieces, weighed and placed in a Waring blendor at once, together with the appropriate solution for the assay. The water content of the kale was determined by the method of the Association of Official Agricultural Chemists.[2] The ascorbic acid was assayed according to the following procedure: Twenty-five gram samples of finely cut kale was submerged directly after weighing in 200 to 250 cc. of filtered 5 per cent metaphosphoric acid solution. All the tissue, extract and washings were transferred to a Waring blendor which was operated for five minutes. The contents of the blendor were transferred to a filter and the liquid filtered with suction through glass wool into a 500 cc. volumetric flask. Washings of the blendor were added to the filter, and the material thereupon was washed with successive portions of 5 per cent metaphosphoric acid until a volume of about 450 cc. was obtained. The filtrate was adjusted to 20 C. and then made up to 500 cc. with acid of the same

From the Massachusetts Agricultural Experiment Station.

Contribution No. 574 of the Massachusetts Agricultural Experiment Station, Massachusetts State College.

1. Gunness, C. I.: Meteorological Records: A Fifty-Year Summary, Bulletin 367, Massachusetts Agricultural Experiment Station, 1939.

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rength and temperature. In order to remove the pigent, 0.5 Gm. of 300 mesh bentonite was shaken for ne minute with 50 cc. of the filtered kale extract in a 00 cc. volumetric flask. The solution was then made to 100 cc. volume with the 5 per cent acid, mixed and tered. The first portion of the filtrate was discarded nd the remainder collected. Twenty cubic centimeter iquots of the filtrate, representing 0.5 Gm. of kale, ere titrated with sodium 2,6-dichlorobenzenoneindoenol dye solution which had been previously standrdized against a standard ascorbic acid solution.

Carotene was determined by the method described by olmes and Spelman.[3]

The nicotinic acid was assayed by the microbiologic ethod of Krehl, Strong and Elvehjem,[4] and the pantoenic acid was determined by the microbiologic produre described by Neal and Strong.[5]

RESULTS

The data obtained from the assay of 18 samles of field-frozen kale are recorded in the table.

sults of Assays of Field-Frozen Kale (Fresh Basis)

m-le o.	Type of Leaf	Water, per Cent	Ascorbic Acid, Mg./ 100 Gm.	Carotene, Mg./ 100 Gm.	Nicotinic Acid, Mg./ 100 Gm.	Pantothenic Acid, Mg./ 100 Gm.
1	Very mature	77.5	156.4	8.0	....	0.74
	Immature	77.5	190.6	5.4	....	0.73
2	Very mature	79.5	179.2	6.8	....	0.72
	Immature	78.0	239.9	6.4	....	0.82
3	Very mature	80.0	120.6	4.9	....	0.80
	Immature	79.0	187.6	3.8	....	0.79
4	Very mature	79.0	183.4	5.8	....	0.75
	Immature	78.0	238.4	7.2	....	0.74
5	Very mature	77.5	141.6	...	2.04	0.71
	Immature	77.5	191.1	...	2.10	0.94
6	Very mature	78.0	195.3	5.7	2.10	0.65
	Immature	77.5	211.6	3.9	2.10	1.25
7	Very mature	78.5	165.5	...	1.88	....
	Immature	78.5	184.2	...	1.96	....
8	Very mature	78.5	147.7	7.2	1.53	0.74
	Immature	78.0	214.4	6.7	2.44	1.11
9	Very mature	77.0	138.1	5.5	2.14	....
	Immature	76.0	251.6	5.8	2.46	....
erage very mature		78.4	158.6	6.3	1.94	0.73
erage immature		77.8	212.2	5.6	2.21	0.91
erage of all		78.1	185.4	6.0	2.08	0.82

dged by these data, the extremely mature ves of kale that had been frozen several times the field contained more carotene but less corbic, nicotinic and pantothenic acids than e immature leaves from the same plants. In study of the influence of supplementary calm and magnesium fertilizers on the nutritive value of kale, Holmes, Crowley and Kuzmeski[6] found essentially the same value for carotene, i. e., 5.8 mg. per hundred grams, as was obtained in this study for 14 samples of field-frozen kale leaves.

A number of investigators have determined the ascorbic acid content of kale. Wheeler, Tressler and King[7] have reported that freshly cut Bloomsdale Double Curled kale contained 150 mg. (fresh basis) and Dwarf German kale 126 mg. per hundred grams. In another study Kirk and Tressler[8] reported that German Dwarf kale leaves contained 117 mg. of ascorbic acid per hundred grams. Burrell and Ebright[9] assayed Scotch kale obtained in the market and found 188 mg. per hundred grams in the autumn and 101 mg. per hundred grams in the winter. Murphy[10] determined the ascorbic acid content of five varieties of kale grown in Maine and found 147 mg. per hundred grams for Dwarf Siberian, 147 mg. for Tall Scotch, 161 mg. for Dwarf Green Curled Scotch, 163 mg. for Norfolk and 189 mg. for Blue Scotch. She also reported that the inner leaves contain 34 per cent more ascorbic acid than the outer leaves from the same plant. These values for fresh nonfrozen kale, which range from 101 to 189 mg. per hundred grams, are somewhat lower than the average values of 158.6 and 212.2 mg. per hundred grams that were obtained in this study of kale that had been frozen several times in the field before it was harvested.

The average values—ascorbic acid, 185.4 mg.; carotene, 6.0 mg.; nicotinic acid, 2.08 mg., and pantothenic acid, 0.82 mg. per hundred grams—obtained for field frozen kale leaves indicate that this is valuable material for the human diet, particularly since kale is almost the only green leafy vegetable grown in this locality that retains high nutritive value even after several freezings in the field.

3. Holmes, A. D., and Spelman, A. F.: Composition Squashes After Winter Storage, Food Research, to published.

4. Krehl, W. A.; Strong, F. M., and Elvehjem, A.: Determination of Nicotinic Acid, Indust. & gin. Chem. (Analyt. Ed.) **15**:471-475, 1943.

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6. Holmes, A. D.; Crowley, L. V., and Kuzmeski, J. W.: Influence of Supplementary Calcium and Magnesium Fertilizers upon the Nutritive Value of Kale, Food Research **10**:401-407, 1945.

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9. Burrell, R. C., and Ebright, V. R.: The Vitamin C Content of Fruits and Vegetables, J. Chem. Educ. **17**:180-182, 1940.

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SUMMARY

Kale is one of the few green leafy vegetables grown in this locality which survives the killing frosts that usually arrive in early autumn. During the following month or two, fresh, growing kale is available for eating either raw or cooked, and the freezing in the field greatly diminishes the characteristic flavor of unfrozen kale that is unpleasant to many people. Eighteen samples of kale that had been frozen at least seven times in the field were assayed for water, ascorbic acid, carotene and nicotinic and pantothenic acid. Mature and immature leaves were tested separately. The average values obtained for the samples were water 78.1 per cent and ascorbic acid 185.4 mg., carotene 6.0 mg., nicotinic acid 2.08 mg. and pantothenic acid 0.82 mg. per hundred grams. These values supply evidence that field-frozen kale can contribute essential nutrients to the human diet, especially when the supply of fresh green leafy vegetables grown in this area is limited.

CONGENITAL DEFECTS FOLLOWING MATERNAL RUBELLA

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AND
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Many theories have been suggested to explain the causation of congenital malformations. A number of observations [1] have been made to support the contention that the environment of the ovum after fertilization can be influenced sufficiently to modify its growth and development. It is, nevertheless, generally accepted that most congenital malformations are due to intrinsic or inherited factors. The evidence that defective germ plasm prior to fertilization of the ovum is responsible for congenital malformations was reviewed by Murphy.[2] He could find no evidence to suggest that malformations result from environmental factors which operate for the first time after fertilization has taken place.

Recently, however, it has been suggested that there is a relationship between certain acute infectious diseases suffered by the mother early in her pregnancy and the development of anomalies in the offspring. Gregg,[3] in 1941, was the first to suggest this, in his report of 78 cases of congenital anomalies in children whose mothers suffered from a virus infection early in their pregnancies. Swan,[4] in 1943 and 1944, reported 43 similar cases. Later, in this country, Reese [5] described 3 cases, Erickson [6] reported 11 and Perera [7] reported 1.

TABLE 1.—*A Summary of Reported Cases of Virus Infection in the Mother During Pregnancy Associated with Congenital Malformations in the Infant*

Investigator	Congenital Anomalies with History of Maternal Virus Disease, No. of Cases	Heart Disease	Unilateral Cataracts	Bilateral Cataracts	Deaf-Mutism	Mental Retardation or Deficiency	Microcephaly	Hypospadias	Microphthalmos	Obliteration of Bile Ducts	Death	Multiple Anomalies
Gregg (1941), Australia	Rubella, 78*	44	16	62	..	78†	..	..	11	..	15	44
Swan (1943).‡	Rubella, 31 Mumps, 1 Influenza, 1	22	5	12	12	4	3	1	..	1	5	15
Swan (1944),‡ Australia	Rubella, 10											
Reese (1944), New York	Rubella, 3	3	1	2	..	..	1	..	1	..	3	3
Erickson (1944), California	Rubella, 11	9	3	7	..	2	..	..	1	..	..	9
Perera (1945), New York	Rubella, 1	1	1	..	..	..	..	..	..	..	..	1
Total.....	136§	79	25	83	12	84	4	1	13	1	23	72

* In 10 of these cases the history of rubella is not definite. Thirteen are from Gregg's own series; the remaining cases from the series of his colleagues.
† Personal communication to Reese.[5]
‡ These two reports include an additional review of 4 cases of congenital anomalies without history of maternal disease, cases of maternal morbilli without congenital anomalies in the offspring and 20 cases of maternal rubella, 4 occurring in third month and the remaining 16 after the first trimester of pregnancy.
§ All cases of maternal rubella occurred in the first trimester of pregnancy except 3 of Swan's, which occurred in the fourth, fifth and sixth months of pregnancy.

From the Department of Pediatrics and Obstetrics, Vanderbilt University School of Medicine.

1. Stockard, C. R.: The Influence of Alcohol and Other Anesthetics on Embryonic Development, Am. J. Anat. **10**:369, 1910. Bagg, H. J.: Disturbances in Mammalian Development Produced by Radium Emanation, ibid. **30**:133, 1932. Murphy, D. P.: The Outcome of 625 Pregnancies in Women Subjected to Pelvic Radium or Roentgen Irradiation, Am. J. Obst. & Gynec. **42**:179 (Aug.) 1929. Warkany, J.: Congenital Malformations Induced by Maternal Nutritional Deficiency, J. Pediat. **25**:476 (Dec.) 1944.

2. Murphy, D. P.: Congenital Malformations, Philadelphia, University of Pennsylvania Press, 1940.

3. Gregg, N. M.: Congenital Cataracts Following German Measles in the Mother, Tr. Ophth. Soc. Australia **3**:35, 1941. Congenital Cataracts Following German Measles in the Mother, editorial, M. J. Australia **2**:651 (Dec. 6) 1941.

4. Swan, C.; Tostevin, A. L.; Moore, B.; Mayo, H., and Black, G. H. B.: Congenital Defects in Infants Following Infectious Diseases During Pregnancy, M. J. Australia **2**:201 (Sept. 11) 1943. Swan, C.; Tostevin, A. L.; Mayo, H., and Black, G. H. B.: Further Observations on Congenital Defects in Infants Following Infectious Diseases During Pregnancy, with Special Reference to Rubella, ibid. **1**:409 (May 6) 1944.

(Footnote continued on next page)

To date, then, 136 cases of congenital anomalis have been reported (summarized in table 1) in which a definite history of a virus infection in the mothers during their pregnancy has been obtained. In all but 2 of these cases the offending virus disease has been rubella. In these 2 exceptions the diseases were mumps and influenza. In all remaining cases the rubella occurred before the third month of pregnancy, with the exception of 3, in which the rubella occurred in the fourth, fifth and sixth months. The congenital anomalies described in these cases are varied. In the total of 136 cases, 80 per cent of the offspring had either unilateral or bilateral cataracts; 62 per cent were found to be mentally deficient; 57 per cent were found to have heart disease; 54 per cent of the total were shown to have the combination of cataracts and heart disease. Other anomalies found in the series were deaf-mutism, mental deficiency, microcephaly, hypospadias, microphthalmos and obliteration of the bile ducts.

It is difficult to evaluate the significance of these reported cases because it is not known how often virus infections occur without congenital malformations or how often malformations occur without virus infections. In other words, there are no controls for the reported cases.

In general, the data required for the solution of this type of problem are those of the fourfold table,[5] such as the following:

	With Anomalies	Without Anomalies	Total Anomalies	Per Cent of Anomalies
With measles				
Without measles				

If the per cent anomalies in the offspring of mothers in the group without measles is the same as that in the offspring of mothers in the group with measles, it can be seen that there is no evidence of a relationship between maternal disease and congenital anomaly; but if the per cent of anomalies in the offspring of mothers with measles is greater than that in the offspring of mothers without measles there is concrete evidence that such a relationship exists.

5. Reese, A. B.: Congenital Cataract and Other Anomalies Following German Measles in the Mother, Am. J. Ophth. **27**:483 (May) 1944.

6. Erickson, C. A.: Rubella Early in Pregnancy Causing Congenital Malformations of the Eyes and Heart, J. Pediat. **25**:281 (Oct.) 1944.

7. Perera, C. A.: Congenital Cataract Following Rubella in the Mother, Am. J. Ophth. **28**:186 (Feb.) 1945.

8. Hill, A. B.: Principles of Medical Statistics, London, The Lancet, Ltd., 1942.

It is impossible to construct such a tab from the data in any of the articles summarize in table 1, although Swan's reports mention ce tain cases of anomalies without maternal di ease.[4]

The purpose of the present study was to su vey the available material and to consider th relationship between measles occurring ear in the pregnancy and congenital malformatio in the light of the preceding discussion.

METHOD OF OBTAINING DATA

In order that we might be able to determi the incidence of anomalies following matern disease and that we might further study th problem, we planned a survey of our hospit records at Vanderbilt University Hospital di rected toward these ends. We reviewed a cases of diagnosed congenital heart disease, co genital cataracts, microphthalmos, deaf-mutis aniridia, hydrocephalus and mongolism seen this hospital during a five year period (19 to 1944). These cases numbered 120.

Method.—Each of the hospital records of these 1 cases was examined for information concerning a virus disease during the pregnancy. A letter and self-addressed card were sent to each mother in t group for information concerning this matter. T letter reads as follows:

VANDERBILT UNIVERSITY
School of Medicine
Nashville, Tennessee

Department of Pediatrics

Dear Mrs.....

We are interested in a follow-up study of your child ....., who was born ..... We have recently learned in our work at Vanderbilt Hospital that certain conditions which you might have had before ..... was born might have been the cause of ..... condition. You can help us greatly and possibly other children by filling in the enclosed card and returning it to us within one week. It will not be necessary for you to sign your name.

Sincerely,

The self-addressed postcard read:

No. .....

Please check (×) if you had any of the following diseases during your pregnancy. Also state at what week or month of your pregnancy this illness occurred.

1. German measles .....; Month .....
2. Whooping cough .....; Month .....
3. Mumps .....; Month .....
4. Did you have any other illnesses or rash during your pregnancy? .....
5. Did you take any sulfa drug during your pregnancy? .....
6. Are there any other children with birth weaknesses or deformities? If so, what kind? .....

Result of Survey.—Sixty-one mothers replied to our questionnaires. In the series of 120 cases of congenital anomalies we found 5 cases in which there was a history of rubella occurring during the pregnancy. In 4 of these 5 cases the disease occurred in the first trimester. In all cases in which we did not receive a reply we considered that the mother did not have rubella. The histories of the 5 cases in which rubella had occurred follow.

REPORT OF CASES [9]

CASE 1.—D. G. B., a white girl, and her twin, born July 29, 1943, are the only two siblings of a 20 year old mother. A diagnosis of rubella was made during the seventh month of her pregnancy. The twin is a normal child. There is no other family history of congenital anomalies. D. was born at "full term." The delivery was normal. Her birth weight was 3 pounds 5 ounces (1,500 Gm.). In the immediate neonatal period the child was described as having two convulsions; however, after the first episode there were no recurrences and she seemed to be in good condition. While there have never been any specific illnesses, the child has never progressed well. Her general development was poor. There was always a feeding problem. D. was first seen in the eye clinic of the Vanderbilt University Hospital outpatient department on June 26, 1944, with the complaint of constant aimless movements of the eyes and a pupillary response to light but not accommodation. Complete cataracts bilaterally were noted. Aplasia of the brain was also suspected. The heart appeared to be normal.

The details of the follow-up of her case are given in table 3.

CASE 2.—A. J. M., a white girl born Nov. 5, 1943, the only sibling of a 26 year old mother. A diagnosis of rubella was made in the sixth week of her pregnancy. There is no family history of other congenital anomalies. A. was born at "full term"; the delivery was normal. Her birth weight was 5 pounds (2,300 Gm.). The immediate neonatal condition was described as "good." The past history of the child reveals that she was rather poorly developed. She was malnourished and always presented a feeding problem. At 2 months of age she had exanthema subitum (Roseola infantum).

A. was first seen when she was admitted to the hospital, on June 8, 1944, with the complaints of "anemia and cataracts." Examination revealed that she had complete cataracts bilaterally. The heart was enlarged, and there was a thrill over the precordium. The rate was rapid, and there was a gallop rhythm. A harsh murmur was heard over the apex, systolic in time, and was transmitted over the entire precordium. A diagnosis of congenital heart disease was made. The hemoglobin content was 11 Gm. The patient was given a transfusion, and a discission of the cataracts was performed. She was discharged to the care of a private physician in another city.

Details of the follow-up are given in table 3.

CASE 3.—C. S., born Sept. 10, 1941, was the last of seven children of a white mother who had rubella during the third month of her pregnancy. He was born at "full term" and had a normal delivery. His birth weight was 8 pounds (3,630 Gm.). The child did not present a definite feeding problem, but he never took his feedings well and was described as fairly well developed and fairly well nourished.

C. was first seen on Feb. 25, 1942, with a severe infection of the upper respiratory tract. He has been followed since that time, and he has a history of similar complaints. Examination revealed mongolism and congenital heart disease. No cataracts were noted.

Details of his follow-up are shown in table 3.

CASE 4.—D. J. R. was born Dec. 7, 1942, the third child of a 32 year old Negro mother who had rubella during the eighth week of gestation. There is no

9. These cases are summarized in table 2.

TABLE 2.—*Clinical Characteristics of Five Cases of Congenital Anomalies Following Maternal Rubella*

Case	Case No.	Mother's Age, Years	Disease During Pregnancy	No. of Months Pregnant at Time of Disease	At Term (T) or Premature (P)	Sex of Child	Race	Birth Weight, Lb., Oz.	Congenital Cataracts	Congenital Heart Disease	Mongolism	Cerebral Aplasia
D. G. B.	1	20	Rubella	7	T*	F	W	3-7*	+	..	..	+
A. J. M.	2	26	Rubella	1½	T*	F	W	5*	+	+	..	+
C. S.	3	..	Rubella	3	T	M	W	8	..	+	+	..
D. J. R.	4	32	Rubella	2	P	F	N	5	+	+	..	+
A. E.	5	21	Rubella	½	T*	F	W	3-6*	+	+	..	+

* The mothers insist that these babies were born after forty weeks of gestation.

TABLE 3.—*Follow-Up of Five Cases of Congenital Anomalies Following Maternal Rubella*

Case	Weight at 7 Mo., Lb.	Weight at 14 Mo. Lb.	Weight at 14 Mo. Oz.	Weight at 30 Mo., Lb.	First Dentition, Mo.	Frequent Infections of the Upper Respiratory Tract	Head Circumference at 7 Mo., Cm.	Head Circumference at 18 Mo., Cm.	Feeding Problem	Malnourishment	Heart Murmur	Searching Movement of Eyeballs	Anemia
1	..	12	3	15	7	+	....	16.5	+	+	No	+	..
2	10	..	..	..	7	..	37.5	....	+	+	Systolic	..	+
3	14	..	..	..	..	+	....	....	Not extreme	Fairly well fed	Systolic	..	..
4	..	6	3	14	..	..	....	Smaller than normal	..	+	Systolic	..	..
5	..	13	14	..	12	..	38	....	Decided	+	Systolic	+	+

family history of congenital anomalies. This child was a premature infant, the birth weight being 5 pounds (2,270 Gm.). The immediate neonatal condition was described as "fair."

D. was first seen on March 31, 1943, because of "her eyes." Examination revealed complete cataracts bilaterally. There was a systolic murmur transmitted over the entire precordium, and the condition was diagnosed as "congenital heart disease."

Details of the follow-up are shown in table 3.

CASE 5.—This baby, born Dec. 12, 1944, is the only child of a 21 year old white mother who had rubella during the second week of gestation. There is no family history of congenital anomalies. This child was a "full term" baby. The delivery was not remarkable. The birth weight was 3 pounds 6 ounces (1,530 Gm.). The infant was seen at 2 months of age (March 1944), at which time she was found to have bilateral congenital cataracts, congenital heart disease and cerebral aplasia.

Details of the follow-up are shown in table 3.

Results.[10]—The occurrence of these 5 instances of rubella among the mothers of the 120 infants having congenital anomalies gives the information necessary to fill in the table with regard to the occurrence of rubella among such mothers. It was our desire in this study to have a comparable control group in which we could consider an equal number of normal babies and investigate those pregnancies for a history of rubella. However, because of the difficulty of establishing such a control group and the impossibility of an adequate follow-up study, we had to seek another means of control. To accomplish this we used the Tennessee Morbidity Statistics.

From the Vital Statistics Data we found that the rate of measles in the female population of the childbearing age group in the area from which our cases are derived (Tennessee) is 0.08 per hundred.[11] If it is assumed that 80 per cent of the cases of measles are not reported,[12] we may then affix a liberal value of 0.4 per hundred for the actual case rate in this area.

The 5 cases in which the mother had a history of measles among our 120 cases of congenital anomalies yields a case rate of 4.2 per hundred in this selected group. It is seen, therefore, that after allowing for the poor reporting of measles (rubeola) and rubella, and assuming that the mothers from whom we received no reply had not had rubella, the rate for our group of mothers is ten times greater than the rate for the population at large. This fact, we feel, adds to the evidence indicating that a relationship exists between maternal rubella and the development of congenital anomalies.

10. Statistical advice in the approach to this problem and the interpretation of the results was given by Dr. Paul Densen.

11. Annual Bulletin of Tennessee Morbidity Statistics, Tennessee Department of Public Health, 1943.

12. Perrott, G. St. J.: The State of the Nation's Health, Ann. Am. Acad. Polit. & Social Sc. **188**:131 (Nov.) 1936.

SURVEY OF MATERNAL RECORDS FOR VIRUS DISEASES, WITH SPECIAL EMPHASIS ON THE PRODUCT OF GESTATION

Various reports in the literature have indicated that certain virus diseases other than rubella may be associated with the development of anomalies. In an effort to investigate this aspect of the problem, we made a survey of all diagnosed antepartum acute infectious diseases seen over a period of one and one-half years (1943 to 1944). These cases numbered 92. Among them 3 were diagnosed as virus diseases. These diseases were rubella, chickenpox and mumps. The cases with a history of maternal virus disease are summarized in table 4. None of these cases are included in previous accounts. The case histories follow:

CASE 6.—This white girl, J. B., was born at term of a 20 year old mother who had rubella in the ninth month of her pregnancy. B. was the result of a normal delivery. The immediate neonatal condition was described as "good." Birth weight was 8½ pounds (3,8 Gm.). There was no congenital anomaly found in the infant.

CASE 7.—J. M., a white boy, was born at term of a 23 year old mother, who had chickenpox in the second week of her pregnancy. Delivery was normal. His immediate neonatal condition was good. His birth weight was 7 pounds (3,175 Gm.). There was no congenital anomaly found in this infant.

CASE 8.—E. C., a "full term" white boy, is the second sibling of a 22 year old mother who suffered from mumps in the eighth month of her pregnancy. The child was delivered without difficulty and weighed 7 pounds 4 ounces (3,790 Gm.) at birth. Immediate neonatal condition was described as "good." Thorough examination of the child revealed no congenital anomalies.

In neither of our series of cases were the mothers followed by us during their virus infections, and consequently we were forced to rely on the records for the diagnoses, as made by the various members of the staff. None of the patients in either series had received any sulfonamide compound which might have produced a rash that could have been confused with rubella.

In all 3 of these instances the children resulting from the pregnancy were normal. The rubella and mumps occurred late in the pregnancy, which fact is in keeping with the previous observations that the disease must usually occur early in order to produce a harmful effect on the fetus. The varicella occurred in the first month and was not followed by congenital anomaly in the child. There have been no previous observations made concerning the relationship between this disease and congenital anomalies (see table 1).

COMMENT

The literature on genetics and experimental embryology contains many references which support the idea that environmental influence in the ovum after fertilization modifies its growth and development. It is not within the scope of this report to review this literature, but to this list, it seems, maternal infection with rubella must be added.

It is extremely interesting to speculate on the possible mechanism whereby maternal disease might produce such pathologic changes in the fetus. In the cases of rubella previously reported there were no virologic assays made, nor has there been reported any experimental work done with the purpose of investigating this problem. Whether the defects in the hearts and lenses of these fetuses are results of blood-borne toxic reactions or of disturbed physiologic processes is still a question.

In July 1944, Swan [14] performed autopsies on 3 infants from his original series and reported the postmortem observations. Clinically he found that the children were small and poorly developed and that all presented feeding problems. All had congenital heart disease, and 2 had congenital cataracts. None of these 3 lived longer than ten weeks. Macroscopic examination of tissues showed that the hearts were enlarged and the auricles were distended. In each child the ductus arteriosus was patent, as was the foramen ovale. The lenses were composed of a central nuclear portion and a peripheral or cortical zone. The nucleus appeared to have undergone necrosis en masse. The nuclear cone was sclerotic and tended to break away from the cortex. Many of the lens fibers had disintegrated and were replaced by vacuoles of varying size. Many of the lens fibers still living showed degenerative changes. The retinas and irises were normal. In the heart there were seen occasional muscle fibers replaced by connective tissue. The kidneys contained an occasional hyalinized glomerulus. The terminal event in the lives of these infants was bronchopneumonia.

Although it has been known for some time that embryonic tissue is highly susceptible to infection, it is difficult to explain this susceptibility. Goodpasture [15] suggested that it may be due to the fact that young and relatively undifferentiated cells are a more propitious medium than mature cells. They may have an undeveloped natural immunity or fetal mechanism for the development of specific immunity may be absent or relatively ineffective. In his study of virus infections in fetal tissue he found that the human chorion has a relatively high resistance to virus infection, with the result that intrauterine infection of the human embryo is relatively rare.

TABLE 4.—*Three Cases of Maternal Virus Infections in the Prenatal Period with Normal Birth Weights and Normal Children*

Case	Case No.	Mother's Age	Disease During Pregnancy	No. of Months Pregnant at Time of Disease	Term (T), Premature (P)	Sex of Child	Race	Birth Weight Lb.	Birth Weight Oz.	Condition of Child
J. B.	6	20	Rubella	8	T	F	W	8	8	Normal
J. M.	7	23	Chickenpox	½	T	M	W	7		Normal
E. C.	8	22	Mumps	8	T	M	W	7	4	Normal

It is of particular interest that the congenital anomalies which follow maternal rubella usually occur very early in the pregnancy. This fact suggests that the virus is capable of producing these changes only on the embryonic or early fetal tissue or perhaps can gain access to these tissues only before the placental barrier is fully developed. During the first two months the optic vesicle is converted into the optic cup, the lens vesicle is removed from the ectoderm and the primordia of the sclera and cornea are laid down. In another month's time, the eye, with the exception of the iris and ciliary body, is completely formed. On the other hand, the development of the cardiovascular system proceeds at a somewhat greater rate, and the septums are fused and the muscle differentiated by the end of the second month. It is quite conceivable that in this very early stage of development the lens and the heart structure have a particular affinity for the virus of rubella.

13. (*a*) Mitchell, A. G., and Fletcher, E. G.: Studies in Varicella, J. A. M. A. **89**:279 (July 23) 1927. (*b*) Tridham, F. C.: Chickenpox During Intra-Uterine Life, Brit. M. J. **1**:1054, 1913. (*c*) Shuman, H. H.: Varicella in the Newborn, Am. J. Dis. Child. **58**:564 (Sept.) 1939.

14. Swan, C.: A Study of Three Infants Dying from Congenital Defects Following Maternal Rubella in the Early Stages of Pregnancy, J. Path. & Bact. **56**:289 (July) 1944.

15. Goodpasture, E. W.: Virus Infection of the Mammalian Fetus, Science **95**:391 (April 17) 1942.

In a review of the literature [16] we could find no mention of congenital anomalies (except for Swan's [4] 2 cases of mumps and influenza) following maternal poliomyelitis, mumps, smallpox, chickenpox, measles (rubeola), influenza or epidemic encephalitis, although we did find frequent reference to intrauterine occurrence of these diseases. This review was unsatisfactory in that the investigators in most instances did not have a careful follow-up study of the infants born to mothers suffering from these diseases.

From the standpoint of preventive pediatrics, the implications of congenital malformation following maternal rubella are tremendous. It would seem too early to do anything more than to speculate concerning the handling of a pregnancy in which exposure to rubella has occurred or in which accurate diagnosis of rubella has been made. Once the disease is diagnosed in the first trimester, the physician must consider the probability of an anomaly in the child. The possibility of a therapeutic abortion has been suggested.[6] The use of human immune globulin following exposure is suggested in order to prevent or modify the disease.

16. Abt, I. A.: Influenza in Newly Born Infant, J. A. M. A. **72**:980 (April 5) 1919. Brahdy, M. D., and Lenarsky, M.: Acute Epidemic Poliomyelitis Complicating Pregnancy, ibid. **101**:195 (July 15) 1933. Cosgrave, A. K.: A Case of Congenital Chickenpox, Malayan M. J. **9**:68 (March) 1934. Harmon, P. H., and Hoyne, A.: Poliomyelitis and Pregnancy, J. A. M. A. **123**:185 (Sept. 25) 1943. Harris, J. W.: Influenza Occurring in Pregnant Women, ibid. **72**:978 (April 5) 1919. Henderson, W. B.: Chickenpox in an Eight-Day-Old Infant, J. Pediat. **4**:668, 1943. Houël and Larribère, J.: Avortemont au cours d'infection ourlienne, Bull. Soc. d'obst. et de gynéc. **18**:410 (June) 1929. Kleinberg, S., and Horwitz, T.: The Obstetric Experience of Women Paralyzed by Acute Anterior Poliomyelitis, Surg., Gynec. & Obst. **72**:58 (Jan.) 1941. Kohn, J. L.: Measles in Newborn Infants (Maternal Infection), J. Pediat. **3**:176 (July) 1933. Kosmak, G. W.: The Occurrence of Epidemic Influenza in Pregnancy, Am. J. Obst. **79**:238 (Feb.) 1919. Miller, N. F.: Anterior Poliomyelitis Complicating Pregnancy, J. Michigan M. Soc. **23**:58 (Feb.) 1924. McGoogan, L. S.: Acute Anterior Poliomyelitis Complicating Pregnancy, Am. J. Obst. & Gynec. **24**:215 (Aug.) 1932. Morrow, J. R., and Luria, S. A.: Pregnancy Complicated by Acute Anterior Poliomyelitis, J. A. M. A. **113**:1561 (Oct. 21) 1939. Puig y Roig, P.: Cas de variole foetale sans variole maternelle, Gynéc. et obst. **6**:176 (Sept.) 1922. Rothwell, W. A.: Smallpox in Utero, Northwest Med. **16**:265 (Sept.) 1917. Roques, F.: Epidemic Encephalitis in Association with Pregnancy, Labour and the Puerperium, J. Obst. & Gynaec., Brit. Emp. **35**:1, 1928. Schell, J. T.: Myelitis Complicating Pregnancy, New York M. J. **83**: 657, 1906. Sinnecker, M.: Beitrag zur Kenntnis der Parotitis im Wochenbett, Zentralbl. f. Gynäk. **51**:2024 (Aug. 6) 1927. Spishakoff, N. M.; Golenternek, D., and Bowen, A. G.: Premature Obstetrical Delivery Due to Poliomyelitis, California & West. Med. **54**:121 (March) 1941. Welz, W. E.: Influenza Complicating Late Pregnancy and Labor, Am. J. Obst. **79**:247 (Feb.) 1919. Footnote 13.

SUMMARY AND CONCLUSIONS

1. One hundred and thirty-four cases have been reported in the literature in which maternal rubella in pregnancy was followed by congenital abnormalities. In all but 3 of these cases the rubella occurred in the first trimester of pregnancy. Congenital cataracts, congenital heart disease and definite mental retardation of the child usually resulted. One case of maternal influenza and 1 of maternal mumps, also occurring in the first trimester, have been reported in the literature, and in the cases in which congenital cataracts were noted in the offspring.

Twenty additional cases of maternal rubella without congenital malformation in the infant have been reported. In 4 of these the rubella occurred in the third month of pregnancy and in the remaining 16 cases it occurred after this.

Seven cases of maternal morbilli (rubeola) without a history of congenital malformation in the infant have been reported in the literature.

2. Five additional cases from our own hospital records, of maternal rubella and congenital abnormalities of the offspring, are reported, in 4 of which the maternal rubella is noted in the first trimester of pregnancy. The 4 infants had congenital heart malformations and mental deficiency, and 3 had congenital cataracts. In the fifth case the mother had rubella at seven months of gestation, and congenital cataracts and cerebral aplasia were noted in the infant.

3. Additional evidence showing that the time of infection and the type of virus disease are important in the outcome of pregnancy is presented as follows: A case of a normal child is reported whose mother had rubella in the ninth month of pregnancy. In 1 case maternal mumps occurred in the eighth month of pregnancy, and in 1 case maternal varicella occurred in the first month of pregnancy. Both children were normal.

4. Further evidence to support the fact that rubella in pregnancy is a predisposing cause of congenital malformation was suggested by a further survey of our records as follows: Maternal rubella was noted in 4.2 per cent of the cases of congenital abnormalities surveyed. This exceeds by at least ten times the actual case rate of maternal rubella for the childbearing age group in the population at large.

5. These associations furnish additional evidence that environmental factors operating for the first time after fertilization of an ovum can cause congenital abnormalities.

TREATMENT OF THE DIABETIC CHILD WITH PARTICULAR REFERENCE TO THE USE OF GLOBIN INSULIN

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Diabetes mellitus in the young patient is so different from diabetes mellitus in the middle-aged or elderly patient that it requires special consideration from a therapeutic standpoint. The majority of children and young adults are undernourished when the disease is first discovered, and the onset of the disease is relatively sudden. The majority of the older patients are obese when the disease is first discovered, and the onset is frequently insidious. The disease in the children, as contrasted to the disease in the adult, is severer. The nutritional requirements for the child are relatively greater and constantly changing, and infections are more frequent and are severer. Exercise is much more erratic, and the emotional pattern is far less stable in childhood. On the basis of these differences, it is safer from the standpoint of practical therapeutics to consider diabetes of the young patient as distinct from diabetes of the middle-aged or elderly patient.

At present there is almost universal agreement that the diet for the child with diabetes mellitus should be essentially the same as for normal children.[1] The need for insulin in treating diabetes in the child is universally recognized. The controversial questions at the present time are:

1. What constitutes an adequate level of control for juvenile patients with diabetes mellitus?
2. Which type of insulin should be employed in order to attain this level of control, a slowly or a rapidly acting insulin or a combination of the two?

Treatment in our clinic has been based on the premises that the diabetic child has normal propensities for health as long as his diabetes is well controlled and that therapy should be based on the maintenance of normal physiologic conditions as far as possible. If the child is treated early and adequately, complete control of the disease can be maintained.[2] The longer the disease is incompletely controlled, the more difficult it will be to attain and maintain complete control. Complete control implies absence of sugar in the urine, absence of insulin reactions and maintenance of an approximately normal blood sugar level. During the periods of study in the hospital, we make frequent observations of the blood sugar levels for experimental purposes, but for clinical evaluation our only criterion for control is to keep the urine as free from sugar as possible without insulin shocks. It is our belief that complete control of the disease will allow normal growth and development and prevent the occurrence of degenerative changes.[3]

The regimen employed by us to attain complete control of the disease consists of the giving of a nutritionally adequate diet, divided into three equicaloric meals, and the administration of amorphous regular insulin. The insulin is given one-half hour before each meal and once during the night, usually at 1 a. m. The distribution of the day's dose among the four injections is approximately 35, 22, 28 and 15 per cent respectively.[2] Although this regimen may seem difficult, because it involves the administration of four injections of regular insulin daily, it has been our experience that the families have been so well pleased with the child's response that they have been very willing to follow this plan.

Burroughs Wellcome & Co., Inc., supplied the globin insulin for this study.

From the Department of Pediatrics, State University of Iowa, and the State Services for Crippled Children, State Board of Education, Children's Hospital.

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2. Jackson, R. L.; Boyd, J. D.; and Smith, T. E.: Stabilization of the Diabetic Child, Am. J. Dis Child. **59**:332 (Feb.) 1940.

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Some clinicians may raise the question of the practicability of our regimen of therapy, which aims to keep the diabetic child free from insulin reactions and free from glycosuria while receiving normal diet even if this requires frequent injections of insulin. We realize that the advantages of a higher level of control have not been indisputably demonstrated. The most notable apparent effect of prolonged hyperglycemia is evidenced by the difference in response between patients who recently have become diabetic and those who have remained mildly glycosuric for some time before complete control is attempted. The latter patients have a much narrower zone of stability and are definitely more difficult to control than patients whose disease has been well controlled soon after the onset of the disease. It is uncommon for any of our well controlled patients to have to be readmitted to the hospital even during relatively severe intercurrent infections. The use of more frequent small injections of insulin allows a greater degree of safety and produces a feeling of security on the part of the mother that she can control the situation. It is our impression that it is a tendency of others to place too much emphasis on the desirability of reducing the number of injections of insulin. The fact that many of the families in this study were hesitant to eliminate the night dose of regular insulin because of their complete satisfaction with the child's condition is evidence that the physician may be more concerned about the number of injections than the parents. Parents' willingness to make some extra effort in order to give their children every opportunity to conserve their health may be underestimated. Our clinical experience has been that it is not only possible but practical to maintain this high level of control for the child who comes from an ordinarily well adjusted home. Although the regimen is rigid at first, the child learns a great deal about his disease and is able gradually to simplify his own care. These children have such a wide range of safety that they frequently remark that they cannot believe there is anything wrong with them. We have felt that these children are making a remarkably good psychologic and sociologic adjustment.

We have not in the past found it possible to use a slowly acting insulin or the combination of a slowly acting insulin and a rapidly acting insulin without having to sacrifice the level of control of the disease. Our results with protamine zinc insulin on the whole have been very unsatisfactory.[4] We have attributed these unsatisfactory results to the duration of action of the protamine zinc insulin, which may exceed twenty-four hours and which consequently may have some cumulative action from day to day. In order to use protamine zinc insulin for the treatment of a juvenile diabetic patient, it is necessary for one to be satisfied with a level of control which permits at least minimal glycosuria as a safeguard against shock. We have not been willing to make this compromise except for the occasional uncooperative patient, whose dietary indiscretions and social habits make a good level of control impossible in any case.

The early clinical reports on globin insulin with zinc, which showed that the duration of its action was definitely less than twenty-four hours and that the major effect had subsided by fourteen to sixteen hours, suggested the possibility of using this type of insulin for the treatment of juvenile patients.[5] It was hoped that we might be able to use the globin insulin with zinc in the evening and thus eliminate the night dose of regular insulin.

METHOD OF HOSPITAL STUDY

Subjects used for study were limited to diabetic children living under controlled conditions in the hospital. A specially trained nursing staff was employed in order to attain accuracy in dosage of insulin, site and depth of injection, standardization of exercise, collection of specimens of urine and recording of any variable factors which arose during the period of study. Competent dietitians were responsible for calculation of diet and weighing and preparation of food. All urine voided was analyzed by laboratory technicians, who also determined the blood sugar levels of the patients throughout the twenty-four hours on two days each week. Samples of blood for estimating blood sugar values were obtained at the following hours: 6 a. m., 7 a. m., 9 a. m., 11 a. m., 4 p. m., 10 p. m., 3 a. m. and 6 a. m.[6] All subjects were emotionally stable, and the amount of exercise was controlled. No infections occurred. Each child underwent a prolonged observation period during which the insulin requirements became constant for the standard conditions imposed by the therapeutic regimen. All subjects remained free both from glycosuria and from clinically significant insulin reactions and maintained approximately normal diurnal blood sugar fluctuations.

4. Jackson, R. L., and Boyd, J. D.: Dangers in the Use of Protamine Zinc Insulin, J. Iowa M. Soc. **28**: 1938.

5. Andrews, G. B., and Groat, W. A.: Globin Insulin: A Clinical Study, New York State J. Med. **40**:913, 1940. Marks, H. E.: A New Globin Insulin: The Importance of Carbohydrate Distribution in the Control of Diabetes with Modified Insulins, M. Clin. North America **24**:649, 1940.

6. A micromodification of the Folin-Wu method was used for estimation of sugar content. The Somogyi method of precipitation was employed.

STUDIES WITH U-20 GLOBIN INSULIN WITH ZINC

For nearly two years the use of U-20 globin insulin with zinc in combination with regular insulin was observed. Thirteen children were used as subjects. A great deal was learned from these observations concerning U-20 globin insulin with zinc, although we have since discontinued its use in favor of U-40 or U-80 globin insulin with zinc. The results of these earlier studies with U-20 globin zinc insulin therefore are given in summary form in order to serve as a background for the studies with U-40 globin insulin with zinc and U-80 globin insulin with zinc. During the control period the subjects received a standard diet given in three equicaloric meals. Amorphous (regular) insulin was administered one-half hour before each meal and once during the night (usually at 1 a. m.). The distribution of the day's dose among four injections approximated 35, 22, 28 and 15 per cent respectively. During one experimental period the same quantity of regular insulin was given at the same time before the morning, noon and evening meals and the remaining 15 per cent of the day's requirement was given as U-20 globin insulin with zinc one-half hour before the evening meal in place of the 1 a. m. dose of regular insulin. This plan proved unsatisfactory because hypoglycemia developed between 3 and 10 p. m., with a gradual rise in the level of blood sugar during the night, so that the fasting level of blood sugar was high (150 to 180 mg. per hundred cubic centimeters). The patients gradually lost their high level of control, and the urine began showing slight traces of sugar. The response was similar to that obtained when three doses of regular insulin were used. Consequently, in another experimental period the regimen was modified by administering one-half hour before the evening meal an amount of globin insulin with zinc equal to the total amount of regular insulin given before the evening meal and during the night (43 per cent of the twenty-four hour total). This plan was fairly satisfactory, and the patients remained under good control. However, the urine occasionally contained a trace of sugar after the evening meal, and the blood sugar values were low in the early evening. In the next experimental period regular insulin was administered one-half hour before the morning and noon meals; the evening and night doses of the previous regimen (43 per cent of the total) were combined and given as U-20 globin insulin with zinc one hour before the evening meal. This modification corrected the slight hyperglycemia and mild glycosuria after the evening meal, but the blood sugar values became low between 8 and 10 p. m. In the last experimental period the size of the evening meal was decreased slightly, and a small lunch was given later, during the early part of the evening. A number of variations of lunches were tried, and it was found that the most satisfactory plan was to give half of the milk from the evening meal (146 calories) as a lunch three hours after the evening meal. Using this plan, we were able to maintain satisfactory control. However, many children require 20 or more units of globin insulin with zinc when this regimen of giving 43 per cent of the day's dose one hour before the evening meal is followed. A request was therefore made for the development of a U-40 globin insulin with zinc which would be comparable in action to commercially available U-80 globin insulin with zinc.

STUDIES WITH U-40 GLOBIN INSULIN WITH ZINC

Hospital Studies.—Ten children, who were hospitalized a total of four hundred and one days for preliminary diabetic regulation, served as subjects for this study. These 10 children were observed an additional one hundred and sixty days after stabilization and received U-40 globin insulin with zinc on eighty-seven of the one hundred and sixty days. The usual procedure was to alternate a control period of one week with an experimental period of one week. During the control period the subjects received a standard diet, given in three equicaloric meals. Amorphous (regular) insulin was administered one-half hour before each meal and once during the night (at 1 a. m.). The distribution of the day's dose among the four injections approximated 35, 22, 28 and 15 per cent respectively. In the experimental period, regular insulin was administered one-half hour before the morning and noon meals; the evening and night doses of the previous regimen (43 per cent of the total) were combined and given as U-40 globin insulin with zinc one hour before the evening meal. Half the milk (146 calories) was taken from this meal and given three hours later. Otherwise the regimens for the control and the experimental group were identical.

During the experimental period the children remained under excellent control. Some of the subjects complained of stinging after the injection of the globin insulin with zinc; otherwise there were no clinical differences noted.

An analysis was made of the diurnal blood sugar values observed on eleven days during the experimental period and of those observed on eleven comparable days during the control period. These blood sugar values are given in table 1, and the means and standard deviations for them are given in table 2. The chart shows the mean values of the blood sugars.

The level of blood sugar maintained during both the control and the experimental period is so close to the physiologic level that for all practical purposes the regimens are interchangeable. The level of blood sugars for each patient is directly related to the amount of insulin given

during the day. Consequently, there is a relatively wide range of values for the different subjects. For example, subjects 1 and 3 had relatively high blood sugar values throughout the day, while subject 6 had low values. If the dose of insulin for subjects 1 and 3 had been slightly higher and the dose for subject 6 somewhat lower, the range of values would have been much narrower. When one examines closely the data for comparable periods, it will be noted that the blood sugar values determined at 3, 6, 7 and 9 a. m. tended to be higher during the experimental period and that the blood sugar values determined at 11 a. m. and 4 p. m. tended to be lower.[7]

There is little doubt that the major action of the U-40 globin insulin with zinc had subsided by the end of fourteen hours, because the blood sugar values determined at 6 a. m. were not significantly different in the control and the experimental periods. However, the fa that the early morning values tended to be high and the 11 a. m. values tended to be lower the experimental period suggests that the glob insulin with zinc may still be acting to a slig degree beyond fourteen hours.

In the control period, when 15 per cent the insulin (amorphous) was administered 1 a. m., there was a relatively sudden fall of t blood sugar level as reflected by the relative low values at 3 a. m. This fall did not occur aft the administration of the globin insulin, but relatively constant level was maintained throug out the early morning hours. There cons quently should be less danger of insulin reactio during the night when globin insulin is employe The more critical period of insulin reactions aft the use of globin insulin with zinc would

TABLE 1.—*Diurnal Blood Sugar Values for Ten Hospitalized Diabetic Patients During a Control and Experimental Period, Each of Eleven Days*

Subject No.	Sex	Age at Onset of Diabetes Mellitus Yr.	Mo.	Duration of Disease at Admission	Insulin Dosage, Units per 24 Hours	Blood Sugar, Mg./100 Cc. Control Period * A. M. 6	7	9	11	P. M. 4	10	A. M. 3	6	Experimental Period * A. M. 6	7	9	11	P. M. 4	10	A. M. 3
1	M	15	2	2 mo.	26	120	110	81	76	82	83	85	90	107	96	107	73	82	68	112
2	F	6	6	1 yr.	33	76	82	80	62	101	120	62	83	88	87	130	67	75	157	62
3	M	12	5	8 mo.	60	124	74	76	83	136	109	67	118	106	101	126	60	100	75	63
3	M	12	5	8 mo.	60	108	157	63	100	...	88	65	137	182	143	143	63	105	150	81
4	F	11	4	1 yr.	29	96	81	86	...	133	120	74	120	113	115	136	54	112	64	69
5	M	15	4	6 wk.	45	...	91	100	81	101	85	65	76	...	...	115	77	75	77	68
6	F	3	4	3 yr.	21	49	38	100	55	112	97	39	46	...	...	87	50	92	56	36
7	F	10	5	1 wk.	23	76	66	103	91	127	126	76	82	126	117	93	79	100	100	68
8	M	15	8	3 wk.	27	102	127	70	74	108	88	76	73	...	133	84	98	128	93	106
9	M	9	2	3 wk.	21	...	...	87	116	...	93	60	77	96	81	91	100	107	80	86
10	F	2	2	10 mo.	40	65	57	108	63	86	78	46	71	70	71	71	57	96	107	90

* During the control period four doses of regular insulin and during the experimental period two doses of regular insu and one dose of U-40 globin insulin with zinc were administered.

TABLE 2.—*Mean and Standard Deviation of the Diurnal Blood Sugar Values of 10 Hospitalized Diabetic Patients, During a Control and an Experimental Period*

Time of Observation	Number of Days	Blood Sugar, Mg/100 Cc. Control Period * Mean	Standard Deviation	Experimental Period * Mean	Standard Deviation
6 a. m.	7	95.0	23.3	113.1	35.3
7 a. m.	8	94.2	34.2	107.9	23.9
9 a. m.	11	86.7	14.5	107.5	24.0
11 a. m.	10	80.1	18.6	72.4	16.6
4 p. m.	9	100.6	19.4	96.0	14.3
10 p. m.	11	98.8	17.0	94.2	33.2
3 a. m.	11	65.0	13.4	76.5	21.6
6 a. m.	10	89.7	27.4	90.7	20.5

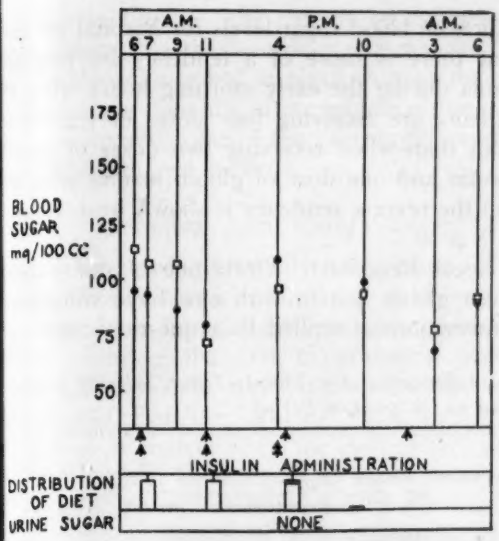
* During the control period four doses of regular insulin and during the experimental period two doses of regular insulin and one of U-40 globin insulin with zinc were administered.

7. Blood sugar values for each child at a given time of day were compared for the experimental and control periods. The test showed the differences in the blood sugar values to be significant at the 7 to 17 per cent level of confidence for observations at 9 a. m., 11 a. m., 4 p. m. and 3 a. m.

in the early hours of the evening (when a lig lunch is given) or between 9 a. m. and 4 p.

Study of the Interchangeability of U-40 a U-80 Globin Insulin with Zinc: Two childr served as subjects for this study. The o difference between the control and the exp mental periods was the strength of globin insu used. U-40 globin insulin with zinc was gi in the control period and U-80 globin insulin w zinc in the experimental period. Regular insu was administered one-half hour before the mo ing meal (35 per cent) and noon meal (22 cent), and globin insulin with zinc (43 per ce one hour before the evening meal. Half milk (146 calories) was taken from the even meal and given three hours later. The blo sugar values are given in table 3.

This short study was done to help evalu the interchangeability of U-40 globin insulin w zinc and U-80 globin insulin with zinc. Th limited data showed no outstanding differenc



The mean of the diurnal blood sugar values of 10 hospitalized diabetic patients observed on eleven days, shown for a control and an experimental period. During the control period four doses of regular insulin and during the experimental two doses of regular insulin and one dose of U-40 globin insulin with zinc were administered. Solid dots and open squares represent the control and the experimental periods, respectively.

contains the children sent home from the hospital on the new regimen. The numbers of children in each group are 4, 32 and 8 respectively.

All our diabetic outpatients routinely keep a daily record showing dosage and distribution of insulin, results of examining four specimens of urine for sugar, insulin shocks, emotional upsets and any variability in exercise or diet. The daily records are summarized for weekly periods and plotted on charts by competent well trained pediatric personnel. These graphic summaries of the child's diabetic history have been used in this study to evaluate his control and progress.

From group II we have selected 23 subjects who had comparable periods on the two regimens. The selection of patients was made on the basis that the children were adhering to the regimens during the periods of study, the mothers could be depended on to keep an accurate record and the patient was in general free from infection. The periods of study for each child did not differ significantly as to time of year or diet. A total of 531 patient-weeks are compared for diabetic regulation as reflected by glycosuria, in-

TABLE 3.—*The Diurnal Blood Sugar Values, Given for 2 Hospitalized Diabetic Patients During a Control and an Experimental Period*

Subject No.	Sex	Age at Onset of Diabetes Mellitus Yr.	Mo.	Duration of Disease at Admission	Insulin Dosage, Units	Blood Sugar, Mg/100 Cc. Control Period * A.M. 6	7	9	11	P.M. 4	10	A.M. 3	6	Experimental Period * A.M. 6	7	9	11	P.M. 4	10	A.M. 3	6
8	M	15	8	3 weeks	27	...	133	84	98	128	93	106	130	...	...	77	70	82	138	107	...
11	F	12	3	10 days	40	78	93	75	68	90	71	65	88	118	117	97	72	104	73	82	...
					40	87	80	68	46	80	73	65	85	96	94	99	68	90	60	84	93

* During the control period two doses of regular insulin and one dose of U-40 globin insulin with zinc and during the experimental period two doses of regular and one dose of U-80 globin insulin with zinc were administered.

Outpatient Study.—Forty-four diabetic children have had their disease controlled by use of the new regimen employing regular insulin before the morning and noon meals and U-40 globin insulin with zinc one hour before the evening meal, with a small lunch three to four hours after the evening meal. These children may be classified into three groups according to the way they were first given globin insulin with zinc: Group I consists of children who had been given a trial in the hospital using globin insulin with zinc and sent home on four doses of regular insulin. After a period of from one to two months of home regulation, they were given globin insulin with zinc. Group II comprises diabetic children whose disease was well regulated at home on four doses of regular insulin and then changed to the new regimen without a period of hospital control. Group III

sulin reaction and insulin dosage. The data for each person are recorded in table 4.

The 12 patients in groups I and III were observed on the new regimen for 760 patient-weeks at home. No loss of diabetic regulation due to the new regimen is recognized.

Shocks: During the control period for the 23 outpatients, there was a total of sixteen mild shocks, three moderate shocks and one severe shock. During the comparable experimental period, there was a total of nineteen mild shocks, one moderate shock and two severe shocks (table 4). These findings do not indicate any clinically significant difference in occurrences of shock during the five hundred and thirty-one weeks of observation. It should be noted that 14 of the 23 subjects had no reactions during the experimental period and that the remaining 9 accounted for the reactions that occurred.

A shock occurred in 1 child at 8:30 p. m. when regular insulin was given by error in place of the globin insulin with zinc. It will be noted also that these well controlled patients living under home conditions averaged only one reaction every six months and that the majority of these reactions were mild.

The data on the time of shock are not complete, and more are available during the recent months when globin insulin with zinc was a part of the regimen than when only regular insulin was used. For the patients in this study, the hour of shock was available for thirty-one occurrences with regular insulin and seventy-nine occurrences when globin insulin with zinc was given in the evening.

The per cent of occurrences of shock for four periods of the day is as follows:

Time	Four Doses Regular Insulin	Two Doses Regular and One Dose Globin Insulin with Zinc
12 a. m. to 4 a. m.	25.8	5.1
5 a. m. to 9 a. m.	9.7	5.1
10 a. m. to 5 p. m.	32.2	63.3
6 p. m. to 11 p. m.	32.2	26.5

The per cent of occurrence of shock during several periods of the day confirms our observation on blood sugar levels for hospital patients that there is more of a tendency for hypoglycemia during the early morning hours when the patients are receiving four doses of regular insulin than when receiving two doses of regular insulin and one dose of globin insulin with zinc and the reverse tendency is shown from 10 a. m. to 5 p. m.

Local Reaction: Thirty-one of our patients given globin insulin with zinc have volunteered information or replied to a question concerning the local reaction to this insulin. Of these patients, 17, or 55 per cent, had no complaint; 10, or 32 per cent, reported some burning, and 4, or 13 per cent, reported considerable discomfort and welts, or both. Apparently most children do not complain or have only minimal discomfort at the injection site when globin zinc insulin is given. However, an occasional child suffers so much discomfort that the advantage of fewer injections for him are outweighed.

Comments: Most of the parents of the children observed in the outclinic studies were hesitant about changing to the new regimen and eliminating the night dose of regular insulin because they were already so secure in car-

TABLE 4.—*Insulin Dosage, Glycosuria, Shock and General Information for Twenty-Three Selected Diabetic Outpatients During a Control and an Observation Period*

Subject No.	Chronologic Age, Years and Months: At Onset of Diabetes Mellitus	When Disease Completely Controlled	When Globin U-40 First Given	Length of Each Observation Period, Weeks	Diabetic Regulation †	Observation Periods *: Control: Range of Insulin Dose, Units	Glycosuria ‡	Shocks: Mild	Moderate	Severe	Experimental: Range of Insulin Dose, Units	Glycosuria ‡	Shocks: Mild	Moderate	Severe	Diet
20	12 7	13 4	14 11	20	G	37-43	0_3	1	0	0	38-41	0_3	2	0	0	Constant
21	2 2	2 3	13 9	42	G	44-61	0_1	7	1	1	44-54	0_1	6	0	0	185 calories less during control for 10 weeks
22	11 7	11 7	16 1	42	E	59-79	0_1	0	0	0	61-68	0_1	0	0	0	Constant
23	9 5	12 5	13 11	22	F	38-43	0_4	0	0	0	38-41	0_4	0	0	0	Constant
24	10 2	10 9	16 2	15	E	56-69	0_4	1	0	0	48-56	0_1	1	1	0	Constant
25	12 2	12 5	13 8	51	E	49-62	0_2	0	0	0	53-78	0_2	0	0	1	Constant
26	1 4	1 5	10 6	15	E	31-33	0_1	0	0	0	31-32	0_1	0	0	0	Constant
27	4 2	4 3	4 11	26	E	8-13	0_2	0	0	0	9-12	0_1	0	0	0	Constant
28	10 10	10 11	13 4	18	E	31-37	0_2	0	0	0	25-27	0_1	0	0	0	Constant
29	8 3	8 3	10 8	20	F	27-28	0_2	0	0	0	31-31	0_2	0	0	0	200 calories higher during control
30	12 10	12 11	14 0	32	E	46-66	0_1	0	0	0	63-66	0_1	0	0	0	185 calories higher during six weeks of experiments
31	10 5	10 5	11 1	4	G	20-27	0_3	0	0	0	26-30	0_3	0	0	0	Constant
32	10 6	12 0	14 1	42	G	20-22	0_2	0	0	0	24-30	0_1	0	0	0	185 calories less control
33	7 8	11 8	15 6	42	G	33-35	0_1	0	0	0	36-42	0_1	0	0	0	185 calories less during control
34	9 4	9 6	12 8	29	E	32-32	0_1	0	0	0	33-34	0_1	0	0	0	Constant
35	10 5	11 5	11 9	15	E	18-26	0_1	0	0	0	19-31	0_1	2	0	0	Constant
36	2 2	3 1	3 5	10	G	10-10	0_1	0	1	0	10-10	0_1	1	0	0	Constant
37	2 3	5 3	5 11	7	F	24-30	0_3	2	0	0	21-28	0_3	3	0	0	Constant
38	2 6	2 10	4 10	17	E	18-20	0_1	0	0	0	22-30	0_1	0	0	0	Constant
39	10 9	10 10	15 3	23	G	53-69	0_2	3	1	0	52-63	0_2	0	0	0	185 calories more during control
40	8 0	8 1	12 4	18	G	44-54	0_1	1	0	0	52-57	0_1	4	0	0	185 calories less during control
41	15 4	15 6	15 9	12	G	26-44	0_1	1	0	0	32-40	0_1	0	0	1	Constant
42	9 6	9 6	13 6	9	F	48-53	0_3	0	0	0	47-54	0_1	0	0	0	Constant

* During the control period four doses of regular insulin and during the experimental period two doses of regular insulin and one dose of U-40 globin insulin with zinc were administered.

† For diabetic regulation E = excellent, G = good and F = fair.

‡ For glycosuria 0_1 = urine specimens free from sugar except for very occasional traces; 0_2 = urine specimens free from sugar except for occasional traces; 0_3 = more than half of the specimens free from sugar but minimal amounts of sugar in the remaining specimens; 0_4 = less than half the specimens free from sugar and minimal amounts of sugar in the remaining specimens.

for their children. The parents of the patients now report that they consider it a definite help to be able to go to bed at night without the care of awakening the child in the middle of the night for insulin, and some of the parents believe that their children rest better.

SUMMARY AND CONCLUSION

A regimen using a rapidly acting insulin along with a slowly acting insulin was developed for well regulated hospitalized juvenile diabetic patients. During the first experimental periods U-20 globin insulin with zinc was used, and it was found that the patients maintained their high level of control when the evening and night doses of regular insulin (43 per cent) were combined and given one hour before the evening meal. As a precaution against hypoglycemia, a small lunch was taken from the evening meal and given three or four hours later.

With moderate and severe diabetes, U-40 globin insulin with zinc was more convenient to give because many of the patients were receiving 20 or more units in the evening under this regimen.

Ten hospitalized patients were observed during a control period and an experimental period. During the control period an adequate diet divided into three equicaloric meals was given, and amorphous regular insulin was administered one-half hour before each meal and once during the night, usually at 1 a. m. During the experimental period the standard diet was given, and regular insulin was administered one-half hour before the morning and noon meals; the evening and night doses of the previous regimen (43 per cent of the total) were combined and given as U-40 globin insulin with zinc one hour before the evening meal, and half the milk was taken from this meal and given three hours later. All the subjects remained under excellent regulation during both periods of observation, and comparative diurnal blood sugar values showed only minor changes. There was a shift in the time of the occurrence of the lower blood sugar values. Whereas the lower blood sugar values were more likely to occur during the early morning hours in the control period, they were more likely to occur during the day, from 11 a. m. to 4 p. m., in the experimental period.

These studies show that the major action of U-40 globin insulin with zinc subsides in from fourteen to sixteen hours, with some action up to as long as eighteen to twenty hours. These observations are in keeping with those of other reports on the duration of action of U-80 globin insulin with zinc.[8]

A study was also made of a group of 23 well regulated diabetic juvenile outpatients for similar control and experimental periods. The results are recorded in table 4. These records show a well regulated group of diabetic children under ordinary home conditions. The change in regimen did not significantly alter their level of control.

It was helpful to the patient and the parents to eliminate the night dose of regular insulin.

This study demonstrates that it is possible and practical to keep diabetic children aglycosuric, except for very occasional traces of sugar in the urine, and free from clinically significant insulin reactions. This level of control can be obtained by the administration of four doses of regular insulin or by two doses of regular insulin and one dose of globin insulin with zinc.

Statistical consultation and helpful suggestions during the preparation of this paper were given by Helen G. Kelly, M.S.

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CAUSES OF PREMATURITY

IV. INFLUENCE OF MATERNAL ILLNESS ON THE INCIDENCE OF PREMATURITY; EMPLOYMENT OF A NEW CRITERION OF PREMATURITY FOR THE NEGRO RACE

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CINCINNATI

Many types of maternal illness occurring during pregnancy have been suggested as predisposing factors leading to premature delivery of infants.[1] It is entirely possible that several abnormal conditions may occur simultaneously in a patient, so that the importance of any one factor may be difficult to assess.

To help clarify this situation, our patients have been separated into groups which would more sharply indicate the influence of single factors on the incidence of prematurity. We selected for the first group mothers whose entire pregnancy, labor and delivery were, as nearly as could be determined, normal. The second group was composed of mothers who suffered one or more illnesses or abnormal conditions during pregnancy. The incidence of premature delivery among the patients of these two groups is discussed in detail in this report. The influence on prematurity rates of each of the most common abnormalities, such as syphilis, toxemia of pregnancy, uterine bleeding and certain other diseases, will be considered separately in subsequent reports. In previous studies [2] the difference of the average birth weight and the gestation period of white and of Negro infants has been demonstrated. In this report, we have employed for the first time a new criterion of prematurity for the Negro infants which permits more accurate racial comparisons.

From the Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati, College of Medicine.

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PROCEDURE

Available for analysis were the records of 13,526 deliveries which took place in the obstetric service of the Cincinnati General Hospital from June 1939 through December 1944. While the mothers were in the hospital, special histories were taken with the objective of the study in mind, and any pertinent information obtained from the examinations or from the observations of the patients in the antepartum clinic or in the hospital was added. The material was coded, and the cards were punched to permit mechanical sorting.

Almost all the patients belonged to economic classes unable to afford the services of a private physician for delivery, although some had visited a family physician for antepartum care. The majority of the women lived in the most congested areas of the city.

Definitions.—A pregnancy was considered normal when the mother was free from symptoms, infections, accidents or abnormalities which could in any way affect the outcome of pregnancy. The physical examination and the laboratory data showed no evidence of acute or chronic disease. A patient was not excluded from the normal group, however, because of mild colds, falls without injury, occasional vomiting or postpartum morbidity. Unfortunately, it was impossible to secure accurate information regarding the diets of the mothers or their nutritional status.

Any infant whose birth weight was less than 5 pounds 8 ounces (2,500 Gm.) was considered to be premature. The use of different standards for the white and the Negro infants seems justified, and this subject will be discussed in detail in a subsequent section of this report.

In accordance with the definition of the American Public Health Association,[3] an infant

3. Year Book, 1935-1936, New York, American Public Health Association, 1936, pp. 244-249.

was considered stillborn if gestation had progressed to the fifth month, that is, to at least one hundred and twenty days, and if the infant showed no evidence of life after birth. Stillborn infants with shorter gestation periods than this were considered abortions and were excluded from consideration in this study.

Multiple pregnancies have not been considered in this report because of the difficulties in interpretation and classification of results. Data for them will be analyzed separately.

RESULTS

Incidence of Premature Births Among White Mothers With and Without Normal Pregnancies.—Of the total number of 7,453 white mothers, 4,043, or 54 per cent, were judged to have had normal pregnancies. Premature deliveries occurred in 5 per cent of this group (table 1), as compared with an incidence of 13 per cent in the group of mothers who had had some illness or abnormal symptoms during the antepartum period. This is a significant difference ($X^2 = 142.4$).

When only the live-born infants were considered, the incidence of prematurity was 5 per cent and 12 per cent respectively. This difference likewise is significant ($X^2 = 104.5$).

One hundred and fifty-nine white infants, or 1 per cent of the entire series, were stillborn. Of this number, 122, or 77 per cent, were born to mothers who had some abnormal condition during pregnancy. Approximately two thirds (64 per cent) of the stillborn infants had been delivered prematurely, and the incidence of premature stillbirths was slightly greater in the group of ill mothers (66 per cent) than in the normal group (57 per cent). This difference is not statistically significant.

Incidence of Prematurity in the Negro Race.—Among the 6,073 Negro women, there were 2,867, or 47 per cent, who had normal pregnancies. The incidence of illness was significantly higher than in the white race ($X^2 = 66.3$). Premature deliveries occurred in 9 per cent of the normal group and in 17 per cent of the mothers

TABLE 1.—*Incidence of Prematurity Among 13,526 Consecutive Single Births*

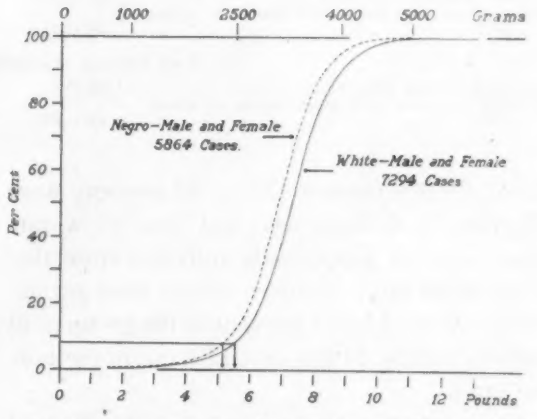
Offspring of Mothers Whose Pregnancies Were Normal Compared with Offspring of Mothers Whose Health Was Impaired

	Live-Born			Stillborn			Live-Born and Stillborn		
	Mothers with Normal Pregnancies	Mothers with Abnormality	Total	Mothers with Normal Pregnancies	Mothers with Abnormality	Total	Mothers with Normal Pregnancies	Mothers with Abnormality	Total
White Race—Criterion of prematurity: birth weight less than 5 pounds 8 ounces (2,500 Gm.)									
Premature...	201 (5)%	379 (12%)	580 (8%)	21 (57%)	81 (66%)	102 (64%)	222 (5%)	460 (13%)	682 (9%)
Full term....	3,805	2,909	6,714	16	41	57	3,821	2,950	6,771
Total.....	4,006	3,288	7,294	37	122	159	4,043	3,410	7,453
Negro Race—Criterion of prematurity: birth weight less than 5 pounds 8 ounces (2,500 Gm.)									
Premature...	244 (9%)	435 (14%)	679 (12%)	19 (54%)	96 (55%)	115 (55%)	263 (9%)	531 (17%)	794 (13%)
Full term....	2,588	2,597	5,185	16	78	94	2,604	2,675	5,279
Total.....	2,832	3,032	5,864	35	174	209	2,867	3,206	6,073

TABLE 2.—*Maternal Morbidity and Premature Birth*

Criterion of prematurity: birth weight less than 5 pounds 8 ounces (2,500 Gm.)

			Premature Births to				
			Mothers with Normal Pregnancies	Mothers with Abnormality	X^2	P	Significance of Observed Difference
White	Live-born and stillborn....	7,453	222 (5%)	460 (13%)	142.4	Very small	Highly significant
	Live born only.....	7,294	201 (5%)	379 (12%)	104.5	Very small	Highly significant
	Stillborn only.....	159	21 (57%)	81 (66%)	1.1	0.28	Not significant
Negro	Live-born and stillborn....	6,073	263 (9%)	531 (17%)	72.7	Very small	Highly significant
	Live-born only.....	5,864	244 (9%)	435 (14%)	47.0	Very small	Highly significant
	Stillborn only.....	209	19 (54%)	96 (55%)	0.009	0.93	Not significant



Cumulative percentage frequencies of birth weights of white and of Negro infants.

with some abnormality of pregnancy (table 1). Considering the live-born infants alone, the respective percentages were 9 and 14. All these figures were considerably higher than those for the white race.

The 209 stillbirths constituted 3.4 per cent of the total series, an incidence of stillbirths significantly higher than in the white race ($X^2 =$

differences in birth weight and gestation peri between white and Negro infants. A light weight Negro infant appears to be as mature a white infant weighing slightly more or, from different viewpoint, a Negro infant compare with a white infant of the same birth weig seems to have reached a more advanced stange maturity.[2b]

TABLE 3.—*Incidence of Prematurity Among 13,526 Consecutive Single Births*

Offspring of Mothers Whose Pregnancies Were Normal Compared with Offspring of Mothers Whose Health Was Impaired

	Live-Born			Stillborn			Live-Born and Stillborn		
	Mothers with Normal Pregnancies	Mothers with Abnormality	Total	Mothers with Normal Pregnancies	Mothers with Abnormality	Total	Mothers with Normal Pregnancies	Mothers with Abnormality	Total
White Race—Criterion of prematurity: birth weight less than 5 pounds 8 ounces (2,500 Gm.)									
Premature...	201 (5%)	379 (12%)	580 (8%)	21 (57%)	81 (66%)	102 (64%)	222 (5%)	460 (13%)	682 (9%
Full term....	3,805	2,909	6,714	16	41	57	3,821	2,950	6,771
Total.....	4,006	3,288	7,294	37	122	159	4,043	3,410	7,453
Negro Race—Criterion of prematurity: birth weight less than 5 pounds 3 ounces (2,350 Gm.)									
Premature...	145 (5%)	314 (10%)	459 (8%)	18 (51%)	87 (50%)	105 (50%)	163 (6%)	401 (13%)	564 (9%
Full term....	2,687	2,718	5,405	17	87	104	2,704	2,805	5,509
Total.....	2,832	3,032	5,864	35	174	209	2,867	3,206	6,073

TABLE 4.—*Maternal Morbidity and Premature Birth*

Criterion of Prematurity: { White race, birth weight less than 5 pounds 8 ounces (2,500 Gm.) / Negro race, birth weight less than 5 pounds 3 ounces (2,350 Gm.) }

			Premature Births to				
			Mothers with Normal Pregnancies	Mothers with Abnormality	X^2	P	Significance of Observed Difference
White	Live-born and stillborn....	7,453	222 (5%)	460 (13%)	142.4	Very small	Highly significa
	Live born only.....	7,294	201 (5%)	379 (12%)	104.5	Very small	Highly significa
	Stillborn only.....	159	21 (57%)	81 (66%)	1.1	0.28	Not significant
Negro	Live-born and stillborn....	6,073	163 (6%)	401 (13%)	141.4	Very small	Highly significa
	Live-born only.....	5,864	145 (5%)	314 (10%)	55.6	Very small	Highly significa
	Stillborn only.....	209	18 (51%)	87 (50%)	0.02	0.88	Not significant

TABLE 5.—*Incidence of Premature Births to White and Negro Women*

	Premature Births to				
	White Mothers	Negro Mothers	X^2	P	Significance of Observed Difference
A: When Same Criterion of Prematurity is Used for Both Races					
Normal maternal histories.....	222 (5%)	263 (9%)	34.9	Very small	Highly significa
Maternal histories with some illness or abnormality	460 (13%)	531 (17%)	12.3	0.0005	Very significant
B: When Different Standards are Used for the Two Races					
Normal maternal histories.....	222 (5%)	163 (6%)	0.12	0.73	Not significant
Maternal histories with some illness or abnormality	460 (13%)	401 (13%)	1.4	0.16	Not significant

21.6). Of this number 174, or 83 per cent, were offspring of mothers who had been ill, a rate which was not significantly different from that of the white race. Stillborn infants were prematurely delivered by 55 per cent of the group of ill mothers and by 54 per cent of those in the normal group.

Reconsideration of the Negro Group.—Several investigators [4] have demonstrated the consistent

In the cumulative percentage curves of bir weight constructed from our own statistics (s chart) the racial difference in birth weig

4. Bakwin, H., and Bakwin, R. M.: Body Build Infants: Anthropometry in the Newborn, Human Bi **6**:612 (Dec.) 1934. Dunham, E. C.; Jenss, R. and Christie, A. U.: Consideration of Race and Sex Relation to the Growth and Development of Infan J. Pediat. **14**:156 (Feb.) 1939. Anderson, Brown a Lyon.[2a]

measured at the level of the mean for the white race is 6.4 ounces (180 Gm.) and at the level of 5 pounds 8 ounces is about 5 ounces (150 Gm.).

It seemed likely that the two racial groups would be more nearly comparable if prematurity for the Negro group were redefined to include only those infants whose birth weights were less than 5 pounds 3 ounces (2,350 Gm). This has been done, and the results appear in table 3. The incidence of prematurity in the two races becomes strikingly similar. Comparative figures for the normal and for the ill mothers of the two races appear in table 4.

COMMENT

When birth weight is used as the standard by which the maturity of an infant is determined, it should be remembered that there are racial differences in average birth weight. If the same standard is used (table 5 *A*) for the two races, an apparent difference is observed in the incidence of premature births in the white and the Negro races. This difference is statistically significant and is true of the births to normal mothers and also to those mothers whose pregnancy has been complicated by some illness or abnormality. It appears that more premature infants are born to Negro women than to white women.

If, however, an arbitrary correction is made to allow for the fact that Negro infants on the average weigh less at birth than do white infants, this apparent difference disappears (table 5 *B*) and the incidence of premature birth in the two races is seen to be very similar.

SUMMARY AND CONCLUSIONS

1. The incidence of prematurity among the offspring of white women who were entirely free from serious infection or other abnormalities during pregnancy was 5.5 per cent. The rate rose to 13.5 per cent among the infants whose mothers had some illness during pregnancy.

2. The incidence of prematurity among the offspring of Negro women was higher, the respective percentages being 9.2 and 16.6. When the criterion of prematurity for Negro infants was adjusted to make their stage of maturity more comparable to that of white infants, these racial differences of incidence disappeared. From our data the lowering of the upper limit of birth weight for prematurity of the Negro infants from 5 pounds 8 ounces (2,500 Gm.) to 5 pounds 3 ounces (2,350 Gm.) seemed to be justified.

With such a classification, the percentage of premature delivery was 5.7 for Negro women with normal pregnancies, as compared with 5.5 for women of the white race. Among the Negro mothers whose pregnancies were complicated by some illness, the percentage of premature delivery was 12.5, as compared with 13.5 among the white mothers.

3. Approximately 80 per cent of the stillborn infants of both races were the offspring of mothers who had had some illness during pregnancy. The majority of stillborn infants were prematurely born (whether or not the mother was in good health during pregnancy).

4. Maternal illness appears to be associated, either directly or indirectly, with about 65 per cent of single live-born premature infants and with 80 per cent of stillborn infants.

5. The relative importance of various illnesses and abnormalities as single predisposing etiologic factors will be the subject of further investigation.

CAUSES OF PREMATURITY

V. INFLUENCE OF SYPHILIS ON THE INCIDENCE OF PREMATURITY

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CINCINNATI

The importance of maternal syphilis as a cause of premature delivery has always been difficult to assess because of several factors which may influence the interpretation of the data. Among these factors are the amount of antisyphilitic treatment the patients have received and the possibility of coexistent diseases which may also induce premature labor. In our previous study [1] the influence of syphilis as a causative factor of prematurity seemed to be of doubtful significance. Since that time more patients have been added to the series, and we have been able to make a more detailed analysis of the subject. These patients could be divided into groups; one composed of women who had no detectable illness of any kind during pregnancy; another including those whose only illness was syphilis, and, finally, groups of women who had other prenatal abnormalities associated with syphilis. The incidence of prematurity among the offspring of the women of these groups was compared, taking into full consideration the amount of antisyphilitic treatment received by the infected mothers. In this manner we have hoped to arrive at a clearer picture of the role played by syphilis as a cause of prematurity.

REVIEW OF THE LITERATURE

Comparisons of the results of previous investigations are often difficult because of different methods of approach to the subject and a lack of uniformity in presenting the results.

The reported incidence of syphilis among the mothers of premature infants has varied from 1.4 to 19 per cent in eighteen different papers previously reviewed by us.[2] In our own preliminary study,[1] we reported the occurrence of syphilis in 8.9 per cent of the mothers of premature infants and in 6.6 per cent of mothers of full term infants, a difference of no statistical significance.

The incidence of syphilis among 3,540 premature infants has been reported by Hess [3] to be 5.1 per cent. In 1,000 autopsies on fetuses and stillborn infants, Adair [4] found that 46 (4.6 per cent) were syphilitic, and the majority of these (78 per cent) had been born prematurely. Of 501 stillborn infants alone, 37, or 7.4 per cent, were syphilitic and 80 per cent had been delivered prematurely.

The incidence of premature deliveries by syphilitic women compared with the incidence among noninfected women has been studied less frequently and is the method of approach in our present report. Jeans and Cooke [5] have reported that 10 (or 2.2 per cent) of a group of 453 syphilitic women delivered their infants prematurely, as compared with 8 (or 0.9 per cent) of a group of 886 nonsyphilitic women. This difference is on the borderline of statistical significance.

The influence of antisyphilitic treatment in prolonging the gestation period has been noted frequently. Among the recent reports is that of McCord,[6] who observed that the incidence of prematurity among the offspring of 2,150 syphilitic women was 23.4 per cent but was only 12 per cent among the offspring of patients who had received ten or more antisyphilitic treatments during pregnancy. Considering both liveborn and stillborn premature infants, he noted

From the Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati, College of Medicine.

1. Anderson, N. A.; Brown, E. W., and Lyon, R. A.: Causes of Prematurity: II. Comparison of Maternal Histories of Premature and of Full Term Infants, Am. J. Dis. Child. **61**:72 (Jan.) 1941.

2. Anderson, N. A., and Lyon, R. A.: Causes of Prematurity: I. Review of the Literature, Am. J. Dis. Child. **58**:586 (Sept.) 1939.

3. Hess, J.: The Premature Infant, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1944, vol. 1, chap. 43.

4. Adair, F. L.: Syphilis of the Fetus and Newborn Infant, Am. J. Obst. & Gynec. **23**:111 (Jan.) 1932.

5. Jeans, P. C., and Cooke, J. V.: Prepubescent Syphilis, New York, D. Appleton and Company, 1930, p. 100.

6. McCord, J. R.: Syphilis and Pregnancy, J. A. M. A. **105**:89 (July 13) 1935.

that 57.6 per cent of the untreated women and only 7.1 per cent of those who had received adequate therapy had premature deliveries. Among 782 syphilitic mothers of premature infants, 67.6 per cent had received no treatment, 19.7 per cent had received less than six treatments and 4.7 per cent had received ten or more treatments.

Wile and Shaw [7] observed that only 10 per cent of 100 well treated syphilitic mothers had premature infants and an additional 3 per cent had delivered premature stillborn infants. Even better results were obtained by Dill and his associates,[8] who emphasized the fact that syphilitic mothers who had been treated before as well as during the pregnancy had the best chances of having living full term infants.

An incidence of stillbirths and abortions as high as 46 per cent among the offspring of women who have recently acquired syphilis has been noted by McKelvey and Turner [9] and Cole and others.[10] With adequate therapy the rates have been reduced to figures varying from 4 to 8 per cent or less.[11]

PROCEDURE AND DEFINITIONS

The histories of 13,526 patients who were admitted to the obstetric wards of the Cincinnati General Hospital during the period from January 1939 through December 1944 were available for study. Each mother was interviewed after the delivery of her infant by a member of the pediatric staff especially interested in obtaining an accurate history. The same pediatricians examined the infants and supervised their care during their stay in the hospital. The pertinent data were assembled on punch cards to permit mechanical sorting. In this study the histories of 197 patients, 96 white and 101 Negro, were incomplete and consequently were excluded, leaving a total of 13,329 for analysis.

The definitions employed are the same as those used in our previous studies.[1]

The Negro infants in this study have been reclassified on the basis of recent observations,[12] which have shown that Negro infants of less birth weight are as mature as white infants of slightly greater birth weight. Our experience has indicated that a difference of about 5 ounces (150 Gm.) occurs in the birth weights of the infants of the two races when measured at the level of the commonly accepted upper limit of prematurity; namely, 5 pounds 8 ounces (2,500 Gm.). We have therefore reclassified the Negro infants to include in the premature classification only those who weighed less than 5 pounds 3 ounces (2,350 Gm.) at birth. In all the tables in this report, the incidence of premature births in the Negro race was first calculated (*a*) as the infants whose birth weight was less than 5 pounds 8 ounces (2,500 Gm.) and then (*b*) as those whose birth weight was less than 5 pounds 3 ounces (2,350 Gm.). We believe that the latter criterion makes possible a more precise comparison with the white race.

The series included large numbers of both the white and the Negro race and in general represented stratums of urban population unable to afford the services of a private physician for the delivery. It is likely that syphilis occurred more frequently in this group than in one of a higher economic level or in the population at large.

The diagnosis of syphilis was made if the Wassermann or Kahn reactions of the blood were definitely positive or if the mother had a past history of syphilis based on a positive serologic reaction. The amount of treatment was estimated from the number of visits to the antisyphilitic clinic rather than from the amount of arsenical or heavy metal administered.

Treatment was considered adequate for the newborn infant if the mother received treatment

7. Wile, U. J., and Shaw, J. W.: Prenatal Treatment of Syphilis with Special Reference to Early Syphilis in the Mother, J. A. M. A. **95**:1791 (Dec. 13) 1930.

8. Dill, L. V.; Stander, H. J., and Isenhour, C. E.: An Evaluation of the Effect of Antenatal Antisyphilitic Therapy on Fetal Mortality and on Congenital Syphilis, Am. J. Obst. & Gynec. **40**:965 (Dec.) 1940.

9. McKelvey, J. L., and Turner, T. B.: Syphilis and Pregnancy: Analysis of Outcome of Pregnancy in Relation to Treatment in 943 Cases, J. A. M. A. **102**: 503 (Feb. 17) 1934.

10. Cole, H. N., and others: Cooperative Clinical Studies in the Treatment of Syphilis: Syphilis in Pregnancy, Ven. Dis. Inform. **17**:39 (Feb.) 1936.

11. Ballantyne, J. W.: Antenatal, Intranatal and Neonatal Death, Brit. M. J. **2**:583 (Sept. 30) 1922. Bartholomew, R. A.: Syphilis as a Complication of Pregnancy in the Negro, J. A. M. A. **83**:172 (July 19) 1924. Armstrong, I.: Control of Venereal Disease in Prenatal Patients, Pub. Health Nurse **21**:574, 1929. Hillis, D. S., and Benensohn, S. J.: Syphilis and Pregnancy, Internat. Abstr. Surg. **66**:54, 1938; in Surg., Gynec. & Obst., January 1938. Halloran, C. R.: Review of the Records of Syphilitic Pregnant Women Treated at the Los Angeles Maternity Service over a Ten-Year Period, Am. J. Obst. & Gynec. **38**:135 (July) 1939. Benensohn, S. J.: Pregnancy in the Syphilitic Mother: Study of 935 Pregnancies at Cook County Hospital, ibid. **43**:508 (March) 1942. Dill, Stander and Isenhour.[8] McKelvey and Turner.[9] Cole and others.[10]

12. Brown, E. W.; Lyon, R. A., and Anderson, N. A.: Causes of Prematurity: IV. Influence of Maternal Illness on the Incidence of Prematurity; Employment of a New Criterion of Prematurity for the Negro Race, Am. J. Dis. Child., this issue, p. 315.

at the beginning of the fifth month of pregnancy or earlier and if she continued to attend the clinic with a fair degree of regularity at weekly intervals until delivery. If more than four treatments were omitted, especially if the lapses occurred consecutively, the therapy was not considered adequate.

Mothers with acquired syphilis who had been treated sufficiently in the past to establish a negative serologic reaction at the onset of pregnancy were still considered to be inadequately treated unless they had received a definite course of therapy during the pregnancy under consideration. Patients with congenital syphilis were placed in a separate group.

about 11 per cent of the mothers of the full term infants. Among the 356 stillborn infants, 210 were prematurely born. Syphilis occurred in 32 per cent of the mothers of these premature stillborn infants and in only 21 per cent of the mothers of the full term stillborn infants. The association of syphilis and premature birth is significant in the separate groups of live-born and of stillborn infants as well as in the combined group.

White Race: The relative incidence of prematurity in the offspring of the syphilitic and the nonsyphilitic groups is compared in table 1. Of the 390 infants of syphilitic white mothers, 54,

TABLE 1.—*Incidence of Prematurity Among Offspring of Syphilitic and Nonsyphilitic Women (Single Births Only)*

	Live-Born			Stillborn			Live-Born and Stillborn		
	Syphilis	No Syphilis	Total	Syphilis	No Syphilis	Total	Syphilis	No Syphilis	Total
White Race—Criterion of prematurity: birth weight less than 5 pounds 8 ounces (2,500 Gm.)									
Premature	37 (10%)	531 (8%)	568 (9%)	17 (89%)	83 (61%)	100 (65%)	54 (14%)	614 (9%)	668 (9%)
Full term	334	6,300	6,634	2	53	55	336	6,353	6,689
Total	371	6,831	7,202	19	136	155	390	6,967	7,357
Negro Race—A. Criterion of prematurity: birth weight less than 5 pounds 8 ounces (2,500 Gm.)									
Premature	157 (14%)	511 (11%)	668 (12%)	50 (63%)	60 (49%)	110 (55%)	207 (17%)	571 (12%)	778 (13%)
Full term	954	4,149	5,103	29	62	91	983	4,211	5,194
Total	1,111	4,660	5,771	79	122	201	1,190	4,782	5,972
Negro Race—B. Criterion of prematurity: birth weight less than 5 pounds 3 ounces (2,350 Gm.)									
Premature	115 (10%)	335 (7%)	450 (8%)	45 (57%)	55 (45%)	100 (50%)	160 (13%)	390 (8%)	550 (9%)
Full term	996	4,325	5,321	34	67	101	1,030	4,392	5,422
Total	1,111	4,660	5,771	79	122	201	1,190	4,782	5,972

RESULTS

Prematurity of the Offspring of Syphilitic and of Nonsyphilitic Women.—In our earlier report, based on an analysis of the histories of 2,514 women, we found that syphilis occurred in about 9 per cent of the mothers of premature infants and in about 7 per cent of the mothers of full term infants and that this difference was not statistically significant. These patients were women who entered the obstetric wards of the Cincinnati General Hospital from July 20, 1938 to July 20, 1939. The present series of 13,329 women includes all patients who entered the obstetric wards of the same hospital for the period beginning Jan. 1, 1939 and ending Dec. 31, 1944. During this period, and notably during the past two years, we have observed an increase in the incidence of syphilis. Syphilis occurred in 18 per cent of the mothers of the premature infants of this series and in about 11 per cent of the mothers of the full term infants. There were 12,973 patients who delivered live-born infants. Syphilis occurred in 16 per cent of the mothers of the premature infants of this group and in

or 14 per cent, were premature, as compared with 614, or 9 per cent, of the 6,967 infants of the nonsyphilitic group.

When the live-born infants were considered alone, the incidence of prematurity associated with maternal syphilis was 10 per cent, as compared with 8 per cent for infants of mothers in the nonsyphilitic group. The higher incidence of prematurity in this instance was not great, and for the live-born infants the difference was not statistically significant.

Of the 155 stillborn infants, 100, or 65 per cent, were classified as premature. Nineteen of the 155 mothers had syphilis, and 17, or 89 per cent of the 19, were mothers of premature stillborn infants.

Negro Race: When the same standard of prematurity was used for the two races (birth weight less than 5 pounds 8 ounces [2,500 Gm.]), 17 per cent of the offspring of syphilitic mothers and 12 per cent of the offspring of nonsyphilitic mothers were found to be premature. When the adjusted standard was used for the Negro infants, the relative percentages were very similar to those for the white race (table 1). The differences oc-

curring in the total group and in the group series of live-born infants were significant.

These differences in the incidence of premature births among syphilitic and nonsyphilitic women have been evaluated by the chi square test of goodness of fit, and the results are shown in table 2.

Incidence of Prematurity Among Offspring of Mothers Whose Only Disease During Pregnancy Was Syphilis.—Tables 1 and 2 do not give an accurate picture of the role played by syphilis in causing premature delivery, partly because many of the mothers in both the syphilitic and the nonsyphilitic group had other illnesses which may have influenced the time of delivery. It seemed desirable, therefore, to compare the incidence of prematurity among the offspring of mothers who had no illness during pregnancy with that of mothers whose only disease was syphilis.

Premature infants were delivered by 222, or 5 per cent, of the 4,043 white mothers who had no detectable abnormality during their pregnancies and by 25, or 10 per cent, of the group of 248 mothers who had syphilis only. Among the live-born infants, prematurity was associated with maternal syphilis for 8 per cent, as compared with an incidence of 5 per cent for the offspring of normal mothers (table 3).

In the Negro race when the same criterion was employed prematurity was noted for the offspring of 9 per cent of the normal mothers and for 13 per cent of those of mothers with syphilis only.

When the classification of prematurity of the Negro infants was changed to include only those whose birth weight was under 5 pounds 3 ounces (2,350 Gm.), the incidence of prematurity became very similar to that of the white race. As in the white race, maternal syphilis appeared to be frequently associated with low birth weight (table 4). Stillborn infants of mothers in the syphilitic group did not seem to be more frequently premature than those of mothers in the nonsyphilitic group.

Comparison of the Incidence of Syphilis and of Prematurity in the White and Negro Races.—In our series, syphilis was far more common in the Negro patients than in the white. The dis-

TABLE 2.—*Maternal Syphilis and Premature Birth*

	Premature Births to				
	Mothers with Syphilis	Mothers with No Syphilis	X^2	P	Significance of Observed Differences
White Race—Criterion of prematurity: birth weight less than 5 pounds 8 ounces (2,500 Gm.)					
Live-born and stillborn	54 (14%)	614 (9%)	11.3	0.0007	Very significant
Live-born only	37 (10%)	531 (8%)	2.3	0.13	Not significant
Stillborn only	17 (80%)	83 (61%)	4.7	0.03	Borderline
Negro Race—A. Criterion of prematurity: birth weight less than 5 pounds 8 ounces (2,500 Gm.)					
Live-born and stillborn	207 (17%)	571 (12%)	25.0	Very small	Very significant
Live-born only	157 (14%)	511 (11%)	8.8	0.003	Significant
Stillborn only	50 (63%)	60 (49%)	3.3	0.08	Borderline
Negro Race—B. Criterion of prematurity: birth weight less than 5 pounds 3 ounces (2,350 Gm.)					
Live-born and stillborn	160 (13%)	390 (8%)	31.9	Very small	Very significant
Live-born only	115 (10%)	335 (7%)	12.5	0.0004	Very significant
Stillborn only	45 (56%)	55 (45%)	2.3	0.13	Not significant

TABLE 3.—*Incidence of Prematurity Among Offspring of "Normal" Mothers and Those Whose Only Illness Was Syphilis (Single Births Only)*

	Live-Born			Stillborn			Live-Born and Stillborn		
	Syphilis Only	"Normal"	Total	Syphilis Only	"Normal"	Total	Syphilis Only	"Normal"	Total
White Race—Criterion of prematurity: birth weight less than 5 pounds 8 ounces (2,500 Gm.)									
Premature	18 (8%)	201 (5%)	219 (5%)	7 (88%)	21 (57%)	28 (62%)	25 (10%)	222 (5%)	247 (6%)
Full term	222	3,805	4,027	1	16	17	223	3,821	4,044
Total	240	4,006	4,246	8	37	45	248	4,043	4,291
Negro Race—A. Criterion of prematurity: birth weight less than 5 pounds 8 ounces (2,500 Gm.)									
Premature	76 (11%)	244 (9%)	320 (9%)	21 (60%)	19 (54%)	40 (57%)	97 (13%)	263 (9%)	360 (10%)
Full term	615	2,588	3,203	14	16	30	629	2,604	3,233
Total	691	2,832	3,523	35	35	70	726	2,867	3,593
Negro Race—B. Criterion of prematurity: birth weight less than 5 pounds 3 ounces (2,350 Gm.)									
Premature	54 (8%)	145 (5%)	199 (6%)	19 (54%)	18 (51%)	37 (53%)	73 (10%)	163 (6%)	236 (7%)
Full term	637	2,687	3,324	16	17	33	653	2,704	3,357
Total	691	2,832	3,523	35	35	70	726	2,867	3,593

ease occurred in more than 25 per cent of the mothers of prematurely born Negro infants and in only 8 per cent of the mothers of premature white infants. We found, however, a difference of like magnitude in the incidence of syphilis in the mothers of white and of Negro full term infants; approximately 5 per cent in the white and 19 per cent in the Negro race. Similar comparisons have been made in the groups of women whose only illness was syphilis (table 5).

From these observations we conclude that the relative incidence of premature births to syphilitic mothers is similar in the two races, and this is especially true when the adjusted standards are used. Nevertheless, if one considers the entire range of diseases which have been assigned as causes of premature birth, syphilis will appear as a cause of prematurity more frequently in the Negro than in the white race.

Influence of Antisyphilitic Treatment.—Congenital syphilis is omitted from this discussion because the number of cases was small. The standards of adequate therapy, which have been described previously, were somewhat higher than those employed by other authors; and only 62, or 16 per cent, of the white syphilitic and 174, or 15 per cent, of the Negro syphilitic patients met the requirements (table 6). Among both the white and the Negro patients, the incidence of premature deliveries was considerably reduced when the mothers received any amount of treatment, adequate or not. The differences of incidence associated with adequate and with inadequate treatment were not significant, but no general conclusion can be drawn from this comparison because the number of subjects were small and our standards of adequacy of therapy were arbitrarily set at high levels.

When the prematurly born Negro infants of less than 5 pounds 3 ounces (2,350 Gm.) and considered as a special class, the incidence of prematurity of the offspring of mothers variously treated was much the same as in the case of the white race (table 6).

The effect of antisyphilitic treatment of the mothers whose only antepartum illness was syphilis has also been determined (table 7). In the case of the white mothers, adequate therapy reduced the incidence of prematurity from 16 per cent among the untreated group to 10 per cent among the treated. Among the Negroes the results were even more striking, since the incidence rate fell from 23 per cent among the untreated group to 6 per cent among the ade-

TABLE 4.—*Syphilis and Premature Birth Among Mothers Whose Only Illness Was Syphilis and Mothers Whose Histories Are Normal*

	Premature Births to				
	Mothers with Syphilis Only	Mothers with No Illness	X^2	P	Significance of Observed Differences
White Race—Criterion of prematurity: birth weight less than 5 pounds 8 ounces (2,500 Gm.)					
Live-born and stillborn	25 (10%)	222 (5%)	9.1	0.002	Significant
Live-born only	18 (8%)	201 (5%)	2.9	0.09	Not significant
Stillborn only	7 (88%)	21 (57%)	1.5	0.22	Not significant
Negro Race—A. Criterion of prematurity: birth weight less than 5 pounds 8 ounces (2,500 Gm.)					
Live-born and stillborn	97 (13%)	263 (9%)	11.3	0.0008	Highly significant
Live-born only	76 (11%)	244 (9%)	3.8	0.05	Borderline
Stillborn only	21 (60%)	19 (54%)	0.06	0.81	Not significant
Negro Race—B. Criterion of prematurity: birth weight less than 5 pounds 3 ounces (2,350 Gm.)					
Live-born and stillborn	73 (10%)	163 (0%)	18.0	0.00002	Very significant
Live-born only	54 (8%)	145 (5%)	7.6	0.006	Significant
Stillborn only	19 (54%)	18 (51%)	0.06	0.81	Not significant

TABLE 5.—*Comparison of Incidence of Premature Births to White and Negro Women Whose Only Illness Was Syphilis*

	Premature Births to				
	White Mothers	Negro Mothers	X^2	P	Significance of Observed Differences
A. White Race—Criterion of prematurity: birth weight less than 5 pounds 8 ounces (2,500 Gm.)					
Live-born and stillborn	25 (10%)	97 (13%)	1.5	0.22	Not significant
Live-born only	18 (8%)	76 (11%)	2.0	0.15	Not significant
Stillborn only	7 (88%)	21 (60%)	1.1	0.28	Not significant
B. Criterion of prematurity { White race: birth weight less than 5 pounds 8 ounces (2,500 Gm.) Negro race: birth weight less than 5 pounds 3 ounces (2,350 Gm.) }					
Live-born and stillborn	25 (10%)	73 (10%)	0.01	0.91	Not significant
Live-born only	18 (8%)	54 (8%)	0.0003	0.98	Not significant
Stillborn only	7 (88%)	19 (54%)	1.8	0.18	Not significant

uately treated, the latter rate being less than that f the normal nonsyphilitic group of mothers (9 er cent). Among the Negro infants who eighed less than 5 pounds 3 ounces (2,350 Gm.) t birth, a prematurity rate of 18 per cent for in- ants of the untreated group of mothers fell to 5 er cent in the adequately treated group.

A low incidence of stillbirths occurred among he adequately treated group of syphilitic moth- ers. Of the total number of 42 stillborn infants mong the offspring of syphilitic women of both aces, only 4 were those of adequately treated atients. A large percentage of the stillborn nfants of the untreated or inadequately treated omen were delivered prematurely.

Incidence of Prematurity Among Syphilitic Women Suffering Some Other Illness During Pregnancy.—A considerable number of syphilitic mothers had some additional illness during pregnancy (table 8). Diseases occurring with syphilis included a variety of conditions, such as toxemia of pregnancy, uterine bleeding, acute infections, tuberculosis, heart disease and other chronic diseases of various kinds. The incidence of premature births was generally higher than normal when the women suffered from other illnesses in addition to syphilis, but the only significant increase in rate occurred when patients also had some type of abnormal uterine bleeding in addition to the syphilitic infection. This problem will be discussed in greater detail in a later paper.

TABLE 6.—*Influence of Antisyphilitic Therapy on the Incidence of Prematurity Among the Offspring of the Entire Group of Syphilitic Women (Exclusive of Congenital Syphilis) (Single Births Only)*

	Live-Born				Stillborn				Live-Born and Stillborn			
	Amount of Treatment				Amount of Treatment				Amount of Treatment			
	None	Inadequate	Adequate	Total	None	Inadequate	Adequate	Total	None	Inadequate	Adequate	Total
White Race—Criterion of Prematurity: birth weight less than 5 pounds 8 ounces (2,500 Gm.)												
Premature	16 (19%)	14 (6%)	7 (11%)	37 (10%)	8 (80%)	9 (100%)	0	17 (89%)	24 (25%)	23 (10%)	7 (11%)	54 (14%)
Full term	69	204	55	328	2	0	0	2	71	204	55	330
Total	85	218	62	365	10	9	0	19	95	227	62	384
Negro Race—A. Criterion of prematurity: birth weight less than 5 pounds 8 ounces (2,500 Gm.)												
Premature	38 (20%)	104 (14%)	14 (9%)	156 (14%)	21 (72%)	21 (55%)	7 (64%)	49 (63%)	59 (26%)	125 (16%)	21 (12%)	205 (17%)
Full term	160	638	149	947	8	17	4	29	168	655	153	976
Total	198	742	163	1,103	29	38	11	78	227	780	174	1,181
Negro Race—B. Criterion of prematurity: birth weight less than 5 pounds 3 ounces (2,350 Gm.)												
Premature	29 (15%)	73 (10%)	12 (7%)	114 (10%)	20 (69%)	20 (53%)	4 (36%)	44 (56%)	49 (22%)	93 (12%)	16 (9%)	158 (13%)
Full term	169	669	151	989	9	18	7	34	178	687	158	1,023
Total	198	742	163	1,103	29	38	11	78	227	780	174	1,181

TABLE 7.—*The Influence of Antisyphilitic Therapy on the Incidence of Prematurity Among the Offspring of a Group of Women Whose Only Illness Was Syphilis (Single Births Only)*

	Live-Born				Stillborn				Live-Born and Stillborn			
	Amount of Treatment				Amount of Treatment				Amount of Treatment			
	None	Inadequate	Adequate	Total	None	Inadequate	Adequate	Total	None	Inadequate	Adequate	Total
White Race—Criterion of prematurity: birth weight less than 5 pounds 8 ounces (2,500 Gm.)												
Premature	6 (12%)	8 (6%)	4 (10%)	18 (8%)	3 (75%)	3 (100%)	0	6 (86%)	9 (16%)	11 (8%)	4 (10%)	24 (10%)
Full term	46	134	37	217	1	0	0	1	47	134	37	218
Total	52	142	41	235	4	3	0	7	56	145	41	242
Negro Race—A. Criterion of prematurity: birth weight less than 5 pounds 8 ounces (2,500 Gm.)												
Premature	19 (17%)	52 (11%)	4 (4%)	75 (11%)	11 (79%)	7 (41%)	3 (75%)	21 (60%)	30 (23%)	59 (12%)	7 (6%)	96 (13%)
Full term	95	415	102	612	3	10	1	14	98	425	103	626
Total	114	467	106	687	14	17	4	35	128	484	110	722
Negro Race—B. Criterion of prematurity: birth weight less than 5 pounds 3 ounces (2,350 Gm.)												
Premature	13 (11%)	37 (8%)	3 (3%)	53 (8%)	10 (71%)	7 (41%)	2 (50%)	19 (54%)	23 (18%)	44 (9%)	5 (5%)	72 (10%)
Full term	101	430	103	634	4	10	2	16	105	440	105	650
Total	114	467	106	687	14	17	4	35	128	484	110	722

SUMMARY AND CONCLUSIONS

1. Prematurity was somewhat more frequently characteristic of the offspring of syphilitic women than of the infants of nonsyphilitic women. For the white race the respective percentages were 14 and 9. For the Negro race they were 17 and 12

per cent, but when the standard of prematurity was adjusted to include as premature only the Negro infants weighing less than 5 pounds 3 ounces (2,350 Gm.) the rates of prematurity were approximately the same as for the white race; namely, 13 and 9 per cent.

2. The influence of maternal syphilis on the prematurity rate was evaluated more precisely by comparing the group of women who had no detectable illness during pregnancy with the group of mothers whose only abnormality was syphilis. Prematurity was noted for 5 per cent of the white mothers who had normal pregnancies and for 10 per cent of those with syphilis only. Among the Negroes, the respective rates were 9 and 13 per cent, but with the adjusted standard of prematurity, the rates among Negroes became 6 and 10 per cent, which were almost identical with the rates observed among the white patients.

3. When the live-born infants were considered as a separate division (omitting the stillborn), the prematurity rate in the white race was slightly but not significantly elevated by the occurrence of maternal syphilis. In the Negro race the difference observed was of statistical significance. Prematurity rates among stillborn infants were not significantly altered by the presence of maternal syphilis. Differences of the same magnitude were noted when the group of mothers who had normal pregnancies was compared with the group of those who had syphilis only.

4. There was a higher incidence of syphilis in the Negro women than in the white. Such a finding has frequently been interpreted to mean that syphilis causes a higher rate of premature delivery for Negro women. Our observations indicate that the incidence of prematurity among syphilitic women was approximately the same for the two races.

TABLE 8.—*Incidence of Prematurity Among the Offspring of Mothers with Some Abnormality in Addition to Syphilis (Single Births Only)*

Health of Mother During Pregnancy	Live-Born			Stillborn			Live-Born and Stillborn		
	Premature	Full Term	Total	Premature	Full Term	Total	Premature	Full Term	Total
White Race—Criterion of prematurity: birth weight less than 5 pounds 8 ounces (2,500 Gm.)									
Syphilis only	18 (8%)	222	240	7 (88%)	1	8	25 (10%)	223	248
Syphilis and bleeding	11 (28%)	28	39	2 (100%)	0	2	13 (32%)	28	41
Syphilis and toxemia	4 (8%)	46	50	6 (86%)	1	7	10 (18%)	47	57
Syphilis, toxemia and bleeding	1 (8%)	11	12	1 (100%)	0	1	2 (15%)	11	13
Syphilis and other abnormality	3 (10%)	27	30	1 (100%)	0	1	4 (13%)	27	31
Total	37 (10%)	334	371	17 (89%)	2	19	54 (14%)	336	390
Negro Race—A. Criterion of prematurity: birth weight less than 5 pounds 8 ounces (2,500 Gm.)									
Syphilis only	76 (11%)	615	691	21 (60%)	14	35	97 (13%)	629	726
Syphilis and bleeding	24 (28%)	63	87	10 (91%)	1	11	34 (35%)	64	98
Syphilis and toxemia	34 (16%)	183	217	11 (55%)	9	20	45 (19%)	192	237
Syphilis, toxemia and bleeding	8 (31%)	18	26	7 (78%)	2	9	15 (43%)	20	35
Syphilis and other abnormality	15 (17%)	75	90	1 (25%)	3	4	16 (17%)	78	94
Total	157 (14%)	954	1,111	50 (63%)	29	79	207 (17%)	983	1,190
Negro Race—B. Criterion of prematurity: birth weight less than 5 pounds 3 ounces (2,350 Gm.)									
Syphilis only	54 (8%)	637	691	19 (54%)	16	35	73 (10%)	653	726
Syphilis and bleeding	22 (25%)	65	87	9 (82%)	2	11	31 (32%)	67	98
Syphilis and toxemia	24 (11%)	193	217	10 (50%)	10	20	34 (14%)	203	237
Syphilis, toxemia and bleeding	7 (27%)	19	26	6 (67%)	3	9	13 (37%)	22	35
Syphilis and other abnormality	8 (9%)	82	90	1 (25%)	3	4	9 (10%)	85	94
Total	115 (10%)	996	1,111	45 (57%)	34	79	160 (13%)	1,030	1,190

5. Specific therapy administered to syphilitic patients during pregnancy had pronounced effects in reducing the rate of prematurity. Among white mothers whose only illness during pregnancy was syphilis, therapy was associated with a drop in prematurity rates from 16 to 10 per cent. Among Negro mothers the rates fell from 23 per cent to 6 per cent.

6. When diseases or abnormal conditions other than uterine bleeding were associated with syphilis during pregnancy, the prematurity rates were slightly but not significantly elevated above those of groups in which syphilis occurred alone. The association of syphilis and conditions producing uterine bleeding resulted in a pronounced increase in the incidence of premature delivery

CHOLECYSTOGRAPHY FOR CHILDREN

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Vague gastrointestinal complaints in children have always been a problem for the pediatrician. With the idea that these symptoms might occasionally be associated with disease of the gallbladder we have often desired to attempt cholecystography, but, owing to the toxic effects which at times follow the use of iodophthalein sodium for adults, it was felt that the use of this medium might be a dangerous procedure, especially for small persons.

Graham and Cole [1] mentioned using cholecystography with iodophthalein sodium for a few children but mentioned no specific age or definite results. John Caffey [2] stated that the youngest patient whose gallbladder was satisfactorily visualized by him with iodophthalein was 3½ years old and that in the few infants examined there was no evidence of accumulation of dye in the biliary tract. Little else on visualization of the gallbladder in children has appeared in the literature. Boyden and Fuller [3] presented a series of cases in which they used iodophthalein by mouth for 41 children between 6 and 11 years of age. They studied primarily size and emptying of the gallbladder, and they made no mention of the percentage of patients whose gallbladders were visualized or of the toxic effects noted.

Apparently a less toxic contrast medium has been achieved with the production by Dohrn and Dietrich of beta (4-hydroxy-3, 5-diiodophenyl) alpha phenylpropionic acid. Since 1940, articles have appeared in the German literature in which this substance was referred to under the trade name of Biliselectan. K. Junkman [4] stated that in toxicity tests on rats the fatal oral dose of Biliselectan is 1.1 Gm. per kilogram, whereas the dose ordinarily used for visualization of the gallbladder is about 0.05 Gm. per kilogram. He further stated that over 50 per cent of this substance is excreted by the kidneys within the first twenty-four hours.

Grunke and Finger,[5] using Biliselectan, noted that they did obtain some negative results in cases of subacute or chronic hepatic damage, but in these cases, filling could not be obtained with iodophthalein sodium injected intravenously. Kleiber [6] also was unable to demonstrate any superiority of iodophthalein over Biliselectan.

Much larger series of cases have been reported in the United States, where this substance is produced commercially as Priodax. Hefke [7] reported a series of 600 attempted visualizations with Priodax. Eighty per cent of the patients had excellent gallbladder shadows and 8 per cent had shadows less intense but considered normal. Toxic effects were mild, namely some nausea and vomiting (8 per cent) and one to three or more loose stools (11 per cent). Three of 100 male patients complained of slight burning on urination. Hefke also stated that Priodax was much better tolerated than iodophthalein sodium, the nausea, vomiting and diarrhea usually associated with the latter being decidedly decreased with the former. Bryan and Pederson [8] reported

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1. Cole, W. H.; Copher, G. H.; Graham, E. A., and Moore, S.: Diseases of the Gallbladder and Bile Ducts, Philadelphia, Lea & Febiger, 1928, p. 322.

2. Golden, R.: Diagnostic Roentgenology, New York, Thos. Nelson & Sons, 1941, vol. 2, p. 965.

3. Boyden, E. A., and Fuller, A. H.: Anatomy and Physiology of Gallbladder in Children: Cholecystographic Study, Am. J. Dis. Child. **48**:565 (Sept.) 1934.

4. Junkman, N, K.: Perorale Cholecystographie mit Biliselectan, Klin. Wchnschr. **20**:125 (Feb. 1) 1941.

5. Grunke, W., and Finger, H.: Cholesystographie mit dem neuen peroralen Kontrastmittel Biliselectan, Klin. Wchnschr. **19**:1187 (Nov. 16) 1940.

6. Kleiber, N.: Zur Frage der peroralen Darstellung der Gallenblase, Deutsche med. Wchnschr. **66**:1134 (Oct. 11) 1940.

7. Hefke, H. W.: Cholecystography with Priodax: A Report on Six Hundred Examinations, Radiology **42**:233 (March) 1944.

8. Bryan, L., and Pederson, N. S.: A New Gallbladder Contrast Medium: Priodax, Radiology **42**:224 (March) 1944.

845 consecutive unselected cases and found "the new preparation to cause much less distress to the patient and to be of considerably more value as a diagnostic contrast medium."

With the knowledge that Priodax was relatively nontoxic, we felt it safe to use even for the youngest infants, and it was the drug used in this series. The technic is simple. It may be summarized as follows: 1. The regular evening meal is given but it contains no fat. 2. Priodax suspended in fruit juice is given about two hours after the evening meal. 3. No breakfast is given, but water is allowed. 4. Roentgenograms are taken at twelve, fourteen and sixteen hours. If the gallbladder is not visualized, the same procedure should be repeated again that evening.

The recommended dose of Priodax is 0.5 Gm. per 10 Kg. of body weight.

As our study progressed, we found that it was frequently necessary to use 1 to 1.5 Gm. per 10 Kg., namely two or three times the recommended dose, in order to get satisfactory results. Included in this paper are data concerning all the patients for whom the drug was tried, even though in the light of later experience we now believe that too small doses might account for a certain percentage of failures. Early in the work, we proceeded carefully, not knowing how infants and smaller children might tolerate larger doses of the drug, a procedure which explains the variations in the dose per kilogram especially in the younger age groups.

TABLE 1.—*Results for Infants Under Six Months*

Patient	Comment	Age, Mo.	Weight, Kg.	Dose, Gm.	Result
M. J.	Infant with mongolism	4 wk.	4	0.25	Negative
D. A. (boy)	Triplet	4	4	0.25 0.25*	Negative
D. A. (girl)	Triplet	4	4	0.37 0.37	Negative
R. A.	Triplet	4	4	0.50 0.50	Negative Negative
V. K.	Osteomyelitis	6	6	0.50 0.75 1.00	Negative Negative Negative
G. B.	Boarder	4	7.2	0.50 0.75	Negative Negative

* Extra value denotes the drug was given again on the following night.

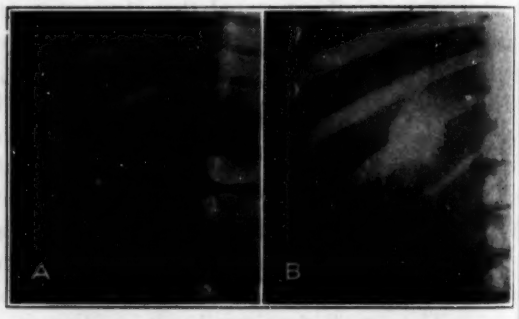
In an attempt to find the best dose of Priodax per kilogram for the various ages, we have arbitrarily divided the entire series of subjects into age groups as follows: under 6 months, 6 to 12 months, 12 to 18 months, 18 to 24 months, 2 to 4 years and over 4 years.

In the group under 6 months of age there were six attempted visualizations with none successful. The infants' ages varied between 1 and 6 months. The dose in this group went as high as 1.6 Gm. per 10 Kg. These infants were fed their regular diets.

TABLE 2.—*Results for Infants Six to Twelve Months Old*

Patient	Comment	Age, Mo.	Weight, Kg.	Dose, Gm.	Result
B. P.	Scurvy	7	6	0.50 0.50 0.50	Negative Negative Negative
M. C.	Boarder	9	6.4	0.50 0.75 1.00	Negative Negative Good
C. G.	Impetigo	10	9	0.50 0.50	Negative Very good
R. R.	Scurvy	11	7	0.375 0.375	Negative Negative

In the group 6 to 12 months old, there were only 4 patients, 1 having good, 1 very good and 2 no visualization. Neither of the patients for whom results were successful had visualization on the first attempt, and Priodax was administered on successive nights. In 1 patient (M. C.) the gallbladder showed no shadow until after three nightly doses, which were increased until the total dose was approximately 1.6 Gm. per 10 kilograms of body weight.



Shadow of gallbladder (*A*) of M. C., 9 months old, and (*B*) of C. G., 10 months old.

TABLE 3.—*Results for Infants Twelve to Eighteen Months Old*

Patient	Comment	Age, Mo.	Weight, Kg.	Dose, Gm.	Result
M. V.	Boarder	12½	6	0.5 0.5 0.5	Negative Negative Negative
J. P.	Diarrhea	13	10	0.5	Excellent
L. S.	Infection of upper respiratory tract	16	9	0.5 0.5	Negative Excellent
L. M.	Old burn	16	11	0.50	Fair

The group 12 to 18 months old included 4 patients, in 1 of whom the gallbladder was visualized only fairly well; 2 others, both of whom were given only ordinary doses (0.5 Gm. per 10 kilograms), had good shadows. There was one failure in this group, in spite of double doses given on three successive nights.

TABLE 4.—*Results for Infants Eighteen to Twenty-Four Months Old*

Patient	Comment	Age, Mo.	Weight, Kg.	Dose, Gm.	Result
D. H.	Burn	19	10	0.50	Negative
				0.75	Negative
		23		0.50	Negative
R. R.	Malnutrition	20	7.2	0.50	Good
J. B.	Burn	21	12.2	0.75	Excellent
L. T.	Cleft palate	22	12	0.75	Negative
				0.75	
				1.00	Negative
E. C.	Infection of upper respiratory tract	23	12.7	0.50	Good

TABLE 5.—*Results for Children Two to Four Years Old*

Patient	Comment	Age, Yr.	Weight, Kg.	Dose, Gm.	Result
B. T.	Tonsillitis	2	11.3	0.50	Negative
				0.50	Negative
				0.50	Negative
				0.50	Negative
				0.50	Negative
R. G.	Tonsillitis	2	12	0.75	Negative
				0.75	Good
P. S.	Bronchopneumonia	2	10	0.50	Negative
L. B.	Burn	2	13.6	0.75	Negative
				0.75	Negative
W. C.	Pharyngitis	2	14	0.75	Excellent
N. C.	Laryngitis	2	12.7	0.50	Negative
E. P.	Urticaria pigmentosa	2½	10	0.50	Negative
				0.75	Faint
				0.75	Excellent
R. A.	Purpura	3	16	1.00	Excellent

Of the 5 patients in this group, 2 had good and 1 excellent gallbladder shadows. In 1 patient (D. H.) the gallbladder failed to visualize though a trial was made again four months after the original attempt. The dose in the latter attempt, however, was probably inadequate. For 1 other patient there was a negative result, even though about double the recommended dose was given.

Visualization in the group 2 to 4 years old was only 50 per cent successful, although two of the unsuccessful attempts for (B. T. and N. C.) probably were due to too small doses and 1 patient (P. S.) was unable to have the cholecystography repeated.

In only 1 of the group over 4 years old did the gallbladder fail to visualize, and this patient was not followed up with a repeated dose. The results obtained in this group suggest that for the most part an ordinary dose (0.5 Gm. per 10 Kg.) is sufficient to obtain satisfactory visualization at these ages.

TABLE 6.—*Results for Children Over Four Years Old*

Patient	Comment	Age, Yr.	Weight, Kg.	Dose, Gm.	Result
B. Mc.	Otitis	4	15	0.50	Negative
				0.75	Excellent
C. G.	Infection of upper respiratory tract	4	15	1.00	Excellent
R. A.	Infection of upper respiratory tract	4	18	1.00	Faint
F. H.	Undiagnosed	4½	17	1.00	Negative
				1.00	Excellent
W. P.	Food poisoning	5	18	1.00	Negative
				1.00	Excellent
J. R.	Undiagnosed	5	21.3	1.25	Excellent
P. D.	Gastroenteritis	5	17	1.00	Negative
A. H.	Adenitis	5	17	0.75	Good
C. L.	Infection of upper respiratory tract	5	15	1.00	Negative
				1.00	Good
A. D.	Malnutrition	5	11.3	0.50	Good
				0.75	Excellent
W. T.	Tonsillitis	5¼	18	1.00	Negative
				1.00	Negative
		5½		1.00	Faint
J. H.	Tonsillitis	6	20	1.00	Excellent
D. Z.	Vincent's angina	6	20	1.00	Excellent
S. N.	Otitis	7	19	1.00	Excellent
J. S.	Atypical pneumonia	7	19.5	1.00	Good
N. F.	Undiagnosed	11	28.6	1.55	Excellent

There were 4 patients for whom the diagnosis of acute catarrhal jaundice was made clinically. The results of the tests on these patients is shown in the following table:

TABLE 7.—*Results for Children with Acute Catarrhal Jaundice*

Patient	Age, Yr.	Dose, Kg.	Onset of Jaundice, Date	Attempted Visualizations			First Successful Visualization	
				Date	Dose, Gm.	Result	Date	Result
B. S.	6	19	7/10/44	7/15/44	1.00	Negative	7/28/44	Fair
				7/16/44	1.00	Negative	8/16/44	Excellent
A. S.	8	26	10/ 5/44	10/12/44	1.25	Negative	11/ 7/44	Faint visualization
J. K.	7	20	10/10/44	.....	....	.....	10/27/44	Good visualization; 1 Gm.
D. R.	5	13.6	11/12/44	11/14/44	0.75	Negative		
				11/15/44	0.75	Negative		
				11/23/44	0.75	Negative		

The earliest visualization (after onset of jaundice) that we were able to obtain was one at seventeen days; one was obtained as late as thirty-three days; 1 patient whose gallbladder did not visualize eleven days after onset of jaundice was unable to have further follow-up.

RECAPITULATION

	Number of Patients	Visualization of Gallbladder Successful	Unsuccessful
Under 6 months	6	0	6
6 to 12 months	4	3	1
12 to 18 months	4	3	1
18 to 24 months	5	3	2
2 to 4 years	8	4	4
4 to 11 years	16	15	1
(With acute catarrhal jaundice)	4	3	1
Total	47	31	16

Percentage of entire series for whom visualization was successful	66
Percentage of patients over 6 months of age for whom visualization was successful	75.6

Toxic effects noted	
Anorexia	1 patient
Loose stools	1 patient (3)
Red blood cells in urine (microscopic)	3 patients
Albuminuria (trace)	1 patient

SUMMARY AND CONCLUSIONS

The results of cholecystography with Priodax for 47 unselected infants and children are reported.

Priodax is a satisfactory contrast medium for infants and children over 9 months of age.

The ordinary dose of 0.5 Gm. per 10 Kg. of body weight is adequate for children over 4 years, but larger dosage, even 1.5 Gm. per 10 Kg., may be necessary for younger children and infants.

Toxic effects are minimal, even in very young infants given two or three times the ordinary dosage.

Further work on infants will be carried out as a later study.

508 North Grand Boulevard.

Case Reports

DERMATITIS EXFOLIATIVA NEONATORUM (RITTER'S DISEASE)

CAPTAIN ARNOLD WIDERMAN
MEDICAL CORPS, ARMY OF THE UNITED STATES

Dermatitis exfoliativa neonatorum (Ritter's disease) has been described as an acute exfoliative and bullous cutaneous disease of unknown cause occurring in newborn infants. An opportunity to observe such a case was presented recently.

REPORT OF A CASE

An 8 day old Negro boy was admitted to this hospital on Feb. 14, 1945, with the following history: He was delivered spontaneously at home on February 6. At birth the physician in charge observed that the child had peculiar sharply demarcated red glazed areas on all four extremities. On the third day the skin sloughed from these sites, leaving hemorrhagic crusted raw surfaces. At the same time, ulcerations appeared over the hard palate and gums. Breast feeding was discontinued. The baby began to have diarrhea shortly afterward.

The antepartum course of the mother was entirely uneventful. This was her fourth child. Serologic reactions of both parents were negative for syphilis and dark field examinations of the lesions on the infant showed no spirochetes. Subsequent tc the child's entry into the hospital, the mother had an abscess of the breast from which a nonhemolytic Staphylococcus albus was cultured.

Examination of the baby on admission revealed the following data. He was in a critical condition. The pulse and respirations were extremely rapid, but the temperature was normal. The defects of the skin and mouth were striking. The skin was absent from the anterior aspects of the legs from the knees to the toes, from the entire left elbow and from both hands. The denuded areas were covered with hemorrhagic crusted matter. In the mouth there were several ulcers covered with adherent, dirty gray exudate. The heart and lungs seemed normal on physical examination. However, the abdomen was moderately distended.

Treatment was instituted as for extensive burns and consisted chiefly of parenteral administration of fluids and plasma and application of warmth. The open lesions were cleansed with warm isotonic solution of sodium chloride, and boric acid ointment dressings were applied. To prevent or counteract infection, large doses of penicillin and sulfamerazine were given (40,000 units of penicillin and 1 Gm. of sulfamerazine daily). Later, penicillin ointment was used in conjunction with the intramuscular therapy. Distention was partially controlled by use of a rectal tube and diarrhea by temporary restriction of oral feedings and by use of protein milk.

In a few days it became evident that the process continued to be active. Bullae appeared and spread over the thighs, abdomen, trunk, back, neck and upper extremities. The following characteristics of the skin were noted: (*a*) repeated or constant trauma by rubbing or pricking with a needle induced formation of bullae, (*b*) the bullae contained clear serous fluid from which Staph. albus could be cultured, (*c*) the bullae were not surrounded by any inflammatory zones but tended to spread and undermine the adjacent seemingly normal skin, (*d*) moderate pressure and rubbing over apparently normal skin removed the pigment portion, leaving a light moist subepithelial layer.

Coincident with the formation of bullae, oral lesions increased in number and severity. Sucking on a rubber nipple appeared to be the inciting factor in their production, but gavage proved to be just as harmful a method of feeding.

The course was progressively downhill. The temperature tended to remain at a subnormal level. Laboratory studies indicated a progressive, moderately severe anemia, with some attempts at regeneration. Culture of the blood yielded Staph. albus despite large doses of penicillin and sulfamerazine. During the last ten days of the infant's life respiratory embarrassment developed; distention became more harassing, and the child died at the age of 31 days.

Autopsy performed one hour after death revealed the following pertinent data: The skin presented the most striking features—epidermolysis, vesiculation and ulceration. Ulceration with exudate was also present in the mouth and nose. The lungs contained little air. The lower lobes of both lungs were atelectatic. Patchy consolidation was present throughout the remaining lobes. In the abdominal cavity, the stomach and small intestines were distended, and the walls were reduced in thickness. In the right retroperitoneal space, there was a well walled-off abscess.

Several sections of skin were submitted for microscopic examination. The following report was made by Capt. Hans Popper, Medical Corps, Army of the United States: "In some areas the epidermis is well developed and reveals a distinct pigmentation of the basal cell layer. In other areas the horny layer is lifted up from the prickle cell layer, or the split runs through the prickle cell layer itself, leaving only a thin lining of the cutis composed of proliferating cells of the basal cell layer. The relatively large bullae thus formed contain detritus and polymorphonuclear leukocytes. In other areas the entire epidermis is missing, and the superficial layers of the corium reveal infiltration by polymorphonuclear leukocytes, histiocytes and a few lymphocytes. The papillary body and the subpapillary layers of the epidermis are edematous. The capillaries are dilated. Around the vessels some scattered lymphocytes are found. In most places the deeper layers of the cutis reveal no changes."

Early lesions were represented by degeneration and separation of the deeper layers of the epidermis resulting in the formation of bullae. Later, there was further destruction of the remaining cell layers of the epidermis.

COMMENT

The cause of dermatitis exfoliativa neonatorum (Ritter's disease) is unknown. Some observers [1] attribute this disease to infection, with staphylococci as the causative agent in most cases. Their contentions are supported by successful results with sulfonamide therapy. Sutton and Sutton [2] have gone so far as to suggest that the disease be included in the impetigo group of streptococcic and staphylococcic infections of the skin.

In the case presented, one can see readily that infection with Staph. albus was prominent throughout. Culture of the blood and of the bullae on the baby, the discovery of a retroperitoneal abscess at autopsy and the abscess on the breast of the mother following nursing of the infant pointed to infection as the etiologic agent.

On the other hand, trauma played an important role. Bullae could be induced by constant pressure of dressings, by repeated friction of one portion of the body on another and by repeated injections with hypodermic needles. Epidermolysis could be demonstrated by rubbing the apparently normal skin with only moderate pressure. A similar situation occurred in the mouth from sucking on a nipple or from gavage. The nasal mucosa was also susceptible to trauma.

The appearance of lesions at birth and the failure of penicillin and sulfamerazine to control the process are points which are not in favor of infection as the etiologic factor. It is also difficult to believe that such extensive cutaneous and mucosal lesions could be induced by Staph. albus in the absence of some fundamental deficiency of the skin and mucous membranes. Observations of Kendall and Aegerter [3] lend supporting evidence. The location of such a deficiency would be probably in the stratum mucosum of the epidermis, for in this Negro child the pigmented layer could be removed, leaving a nonpigmented dermis. Histologic sections of early lesions place the difficulty within the cell layers of the epidermis.

SUMMARY AND CONCLUSIONS

The evidence is at hand that dermatitis exfoliativa neonatorum (Ritter's disease) is a cutaneous affliction of the newborn with symptoms of exfoliation, vesiculation, and epidermolysis that can be induced by trauma. The part played by infection is difficult to evaluate and may be a secondary factor similar to that found in cases of extensive burns, in which destruction of the cutaneous barrier permits invasion by common bacteria. The etiologic basis for the disease arises probably in some deficiency of the epidermis. More specific dermatologic definition is required to exclude cases of impetigo and dermatitis desquamativa (Leiner) from the category of this disease. Lack of such clarity may result in mistaken claims of cure. It appears likely that the prognosis of dermatitis exfoliativa neonatorum depends chiefly on the extent of actual and potential loss of cutaneous surface.

1. Bell, D., and Woods, A. W.: A Case of Exfoliative Dermatitis of the Newborn (Ritter's Disease), Arch. Dis. Childhood **17**:157 (Sept.) 1942. Ryan, N. W., and Goldman, L.: Treatment of Ritter's Disease with Sulfapyridine, Am. J. Dis. Child. **59**:1057 (May) 1940.

2. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, St. Louis, C. V. Mosby Company, 1939, pp. 910-911.

3. Kendall, N., and Aegerter, E. E.: Ritter's Disease, J. Pediat. **15**:733 (Nov.) 1939.

SALICYLATE INTOXICATION IN CHILDREN

REPORT OF FOUR CASES

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Since the recent advent of massive salicylate therapy [1] in the treatment of rheumatic fever, a number of cases of salicylate poisoning associated with this form of treatment have been reported.[2] In this communication 4 cases of salicylate intoxication in children are presented, in 3 of which the condition developed during intensive salicylate therapy for acute rheumatic fever and in the fourth following the accidental ingestion of methyl salicylate.

REPORT OF CASES

CASE 1.—J. W., a 10 year old white boy, was admitted to the hospital Aug. 4, 1444, with a history of four days of sore throat, acute severe generalized polyarthritis and fever but with no definite history of administration of salicylates. No previous attacks of polyarthritis had been experienced, but sore throats had been frequent during the past year. At the time of his admission, the temperature was 103 F., pulse rate 116 and respiratory rate 35. The heart was of normal size (confirmed roentgenologically), with regular sinus rhythm, but a blowing apical systolic murmur transmitted to the aortic area and a definite harsh pulmonic systolic murmur were present. The sedimentation rate (Wintrobe) was 30 mm. per hour, erythrocytes numbered 3,040,000 and leukocytes 14,800 per cubic millimeter; the streptococcus antifibrinolysin activity was 2 plus, and the urine was normal. A roentgenogram of the chest revealed no abnormal pulmonary conditions.

Salicylate therapy was instituted on the patient's second day in the hospital, a total of 6 Gm. of sodium salicylate being given intravenously in twenty-four hours (0.15 Gm. per kilogram of body weight). The same amount was given orally as enteric-coated tablets on the third day. By the fourth day, the polyarthritis had improved remarkably, but otherwise the general condition was worse, the sedimentation rate being 34 mm. per hour and the electrocardiogram showing an alternate 3:1 and 4:1 heart block. A mild degree of dyspnea was observed but was attributed to cardiac decompensation. The patient was mentally confused and irritable and vomited several times. Nevertheless, because of the clinical impression that the carditis was becoming more severe, therapy by the intravenous route was repeated on the fourth and fifth hospital days. However, by the afternoon of the fifth day it was realized that the dyspnea might actually be hyperpnea due to salicylate intoxication. A carbon dioxide–combining power of 14 volumes per cent at the time substantiated this interpretation. Therapy was started immediately, one sixth molar sodium lactate solution being given intravenously, with a resultant rise in the carbon dioxide–combining power to 20 volumes per cent within three hours. Despite the relief of hyperpnea by this treatment, pulmonary edema with signs of circulatory failure developed, and the patient died four hours after the intravenous injection.

During treatment with sodium salicylate, blood was drawn daily for the determination of salicylate concentration, but, because we were not prepared to do this procedure at this time, the samples were sent to a New York city hospital for analysis. Unfortunately, the reports did not reach us until the patient was dying. The daily blood levels were 360, 420, 810 and 1,004 micrograms per cubic centimeter.[3]

Autopsy.—Necropsy was performed two and one-half hours after death. The body weighed 90 pounds (41 Kg.), measured 55 inches (137.5 cm.) and exhibited no unusual external changes.

Petechial hemorrhages were the outstanding gross abnormalities. These were numerous and were found in the mesentery of the small intestine, beneath the parietal peritoneum and the lining of the pericardial cavity, within the subcapsular region of the thymus and the adrenal glands and in the subepicardial fat. The abdominal cavity contained 200 cc. of clear, straw-colored fluid, and the pericardial cavity was distended with 100 cc. of slightly turbid, light amber fluid interspersed with delicate strands of fibrin.

The heart was slightly enlarged and showed slight dilatation of its right side and of the mitral ring. Along the line of closure of the mitral leaflets and extending down over some of the chordae tendinae were tiny smooth opalescent verrucae. Microscopically an acute active pancarditis was found. Within the auriculoventricular node there were several Aschoff bodies and a small artery greatly altered by rheumatic arteritis.

The lungs were slightly increased in weight, and their external surfaces were pink but mottled with several small dark red atelectatic foci. The cut sur-

From the Department of Pediatrics, Union University, Albany Medical College and Albany Hospital.

1. Coburn, A. F.: Salicylate Therapy in Rheumatic Fever: A Rational Technique, Bull. Johns Hopkins Hosp. **73**:435-464 (Dec.) 1943.

2. (*a*) Ashworth, C. T., and McKemie, J. F.: Hemorrhagic Complications, with Death, Probably from Salicylate Therapy, J. A. M. A. **126**:806-810 (Nov. 25) 1944. (*b*) Kaiser, A. J.: Personal communication to the authors. (*c*) Fashena, G. J., and Walker, J. N.: Salicylate Intoxication: Studies on the Effects of Sodium Salicylate on Prothrombin Time and Alkali Reserve, Am. J. Dis. Child. **68**:369-375 (Dec.) 1944.

3. These and the other blood salicylate values were determined by the method of Brodie, B. B.; Udenfriend, S., and Coburn, A. F.: Determination of Salicylic Acid in Plasma, J. Pharmacol. & Exper. Therap. **80**: 114-117 (Jan.) 1944.

faces were also mottled red and pink and exuded frothy blood-tinged fluid. Similar fluid filled the bronchial lumens. On microscopic examination early acute bronchitis, severe pulmonary edema, extreme congestion and a few small perivascular hemorrhages within the interlobular septums were seen.

Though no gross changes were discovered in the kidneys, microscopic examination disclosed an unusual type of edema limited to the convoluted tubules. The edema fluid was observed between the lining epithelial cells as well as beneath them and in some locations had accumulated in such quantities that it completely and widely separated the cells from their basement membrane. All the lining cells of the tubules showed extreme parenchymatous degeneration. These changes suggested an early nephrosis.

Sections from two of the metatarsophalangeal joints revealed foci of fibrinoid degeneration, proliferation of fibroblasts and infiltration with mononuclear cells. These lesions were similar to those seen in the mitral valve.

Examination of the brain and spinal cord was not permitted.

Anatomic Diagnoses.—The final diagnoses were as follows: (1) active rheumatic pancarditis, with dilatation of the right auricle and ventricle and tricuspid and mitral rings; (2) pericardial effusion; (3) acute passive congestion of the lungs; (4) acute bronchitis; (5) pulmonary edema; (6) active rheumatic arthritis; (7) intoxication due to salicylates; (8) hemorrhages into the mesentery, thymus and adrenal glands, epicardium, peritoneum and pericardial sac; (9) acidosis (based on clinical observations), and (10) nephrosis of undetermined type.

CASE 2.—R. H., a 9 year old white boy, was admitted to the hospital Sept. 5, 1944, because of anorexia and weakness of three weeks' duration. In March 1944 he had scarlet fever, which was followed three weeks later by migrating polyarthritis. Treatment had consisted only of sporadic rest in bed. Hospitalization was advised after several months, when his physician discovered that a heart murmur had developed.

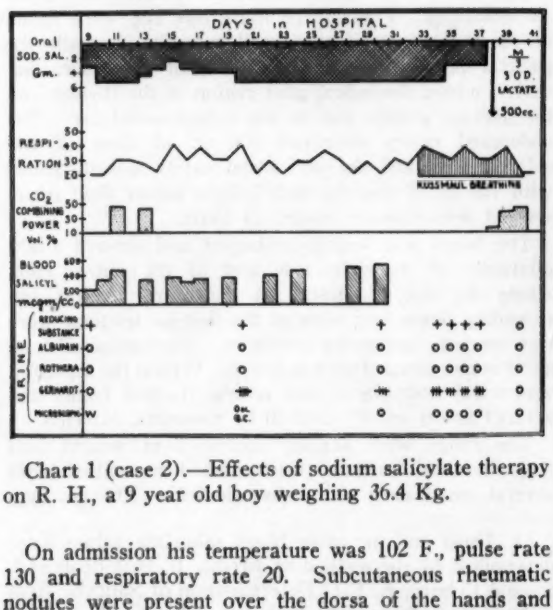

Chart 1 (case 2).—Effects of sodium salicylate therapy on R. H., a 9 year old boy weighing 36.4 Kg.

On admission his temperature was 102 F., pulse rate 130 and respiratory rate 20. Subcutaneous rheumatic nodules were present over the dorsa of the hands and about the elbows. There was decided cardiac enlargement, and a loud blowing systolic murmur could be heard over the entire precordium. The cardiac enlargement was verified roentgenologically (greate cardiac diameter 14.2 cm.), but no significant change were disclosed by the electrocardiogram. The sedime tation rate (Wintrobe) was 24 mm. per hour; the leuko cytes numbered 23,700 and the erythrocytes 4,400,00 per cubic millimeter; the streptococcus antifibrinolysi activity was 3 plus, and the urine was normal.

Although the child was suffering from chronic acti rheumatic fever, it was decided, because of the seve carditis, to administer massive salicylate therapy (cha 1). In view of our previous experience, only 0.1 G per kilogram of sodium salicylate was given orally i the form of enteric-coated tablets during the first twenty four hours. This dose resulted in a blood salicyla level of 200 micrograms per cubic centimeter. Since level of 350 micrograms per cubic centimeter was de sired, the dose was increased the next two days t 0.15 Gm. per kilogram, and at the end of this tim the blood salicylate level had risen to 430 microgram per cubic centimeter. The daily intake of the dru during the next eight days was frequently adjuste the blood level being used as a guide, but it was foun impossible to maintain a level of 350 micrograms p cubic centimeter with less than 0.15 Gm. per kilogra per day. Therefore, this dose was continued for th next twelve days without clinical signs of salicyla intoxication or evidences of clinical improvement exce for the disappearance of the rheumatic nodules. Durin the following six days, gradually increasing hyperpn mental depression and lethargy were noted, and th dose of salicylates was reduced to 0.1 Gm. per kil gram. Since no further clinical improvement wa observed and the drug apparently was producing ear intoxication, its use was discontinued on the thirty seventh hospital day. The carbon dioxide-combinin power at this time was 18 volumes per cent. Th acidosis, as measured by the carbon dioxide-combini power, responded promptly to intravenously administere sodium lactate and orally administered sodium bica bonate. The highest blood salicylate level observe during the course of treatment was 550 micrograms p cubic centimeter on the thirtieth hospital day, a lev which in all previous reports has been considered belo the toxic level for young adults. In this case the develo ment of salicylate intoxication had been insidious and h occurred with what was considered adequate clinic and laboratory control. Another interesting feature w noted during the course of drug therapy, a 1 pl reduction of Benedict's solution by some reducing su stances in the urine.

The greatest cardiac diameter by roentgenogram w reduced from 14.2 to 12.2 cm. during the initial sta of treatment, but after the intoxication it increased t 13.9 cm. An apical presystolic murmur had develop during treatment and was confirmed by stethogra At the termination of administration of salicylat roentgenologic examination of the lungs showed in th upper lobe of the right lung a focus of irregular co solidation which could not be confirmed on clinic examination. Cultures of materials from the thro at this time yielded a hemolytic streptococcus and pneumococcus which could not be typed. The sed mentation rate was then 28 mm. Two months later was 36 mm., the roentgenogram of the chest show complete clearing of the previous irregular area consolidation in the upper lobe of the right lung a the greatest cardiac diameter was 13.2 cm., which w 1 cm. less than that on admission.

CASE 3.—J. T., an 11 year old white girl, was a mitted to the hospital Dec. 1, 1944, with a history

tive rheumatic fever and polyarthritis of four months' ration. Three days before admission she had an acerbation of her illness. On the first day of this isode, her physician prescribed sodium salicylate orally the form of enteric-coated tablets, 0.15 Gm. per kilo- am for twenty-four hours, increased the amount 0.3 Gm. per kilogram on the second day and duced it to 0.25 Gm. per kilogram on the third and rth days, but only about half of the last day's dose was tained. At the end of the first day of treatment, vomit- , epistaxis and dyspnea occurred. These symptoms in- eased in severity each day and were regarded by physician as manifestations of the rheumatic process, st as we had regarded them in our first case. On patient's admission to the hospital a diagnosis of te salicylate intoxication was made (chart 2).

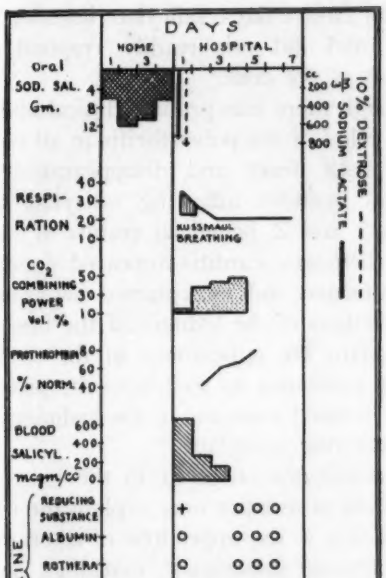

Chart 2 (case 3).—Effects of sodium salicylate therapy J. T., an 11 year old girl weighing 40 Kg.

Her temperature on admission was 100.4 F., her pulse e 132 and her respiratory rate 26. Severe hyperpnea ussmaul in type), drowsiness, dehydration and a t apical systolic murmur were noted. The urine owed a 1 plus reduction of Benedict's solution on first day only; no ketones were present in the urine the first three days, but the Gerhardt test gave a p purple color characteristic of salicylates. The throcytes numbered 4,500,000 and the leukocytes 250 per cubic millimeter. The sedimentation rate Vintrobe) was 16 mm. per hour, and the carbon xide-combining power was 10 volumes per cent. abnormal changes were seen in the electrocardio- m. A roentgen examination of the chest disclosed normal-sized heart with a slight bulge in the left ficle, interpreted as being consistent with mitral nosis, and an accentuation of the pulmonary mark- s in the midportion bilaterally. Hemolytic strepto- ci were isolated from the throat. The blood salicylate el at the time of admission was 640 micrograms per ic centimeter. She was given treatment consisting one-sixth molar and one-third molar solutions of ium lactate, 10 per cent solution of dextrose given intravenously, vitamin K intramuscularly and vitamins B and C and fluids orally. She responded well to treatment as evidenced by a rise in the carbon dioxide-combining power to 37.2 volumes per cent and disappearance of hyperpnea within twenty-four hours. Epistaxis occurred twice within the first twenty-four hours. The prothrombin times,[4] determined daily beginning on the second day and expressed in percentage of normal, were 40, 60, 65 and 80 per cent. The blood salicylate level on the second day was 250 micrograms per cubic centimeter and on the third day 115 micrograms per cubic centimeter. She was discharged on the seventh hospital day completely recovered from the salicylate intoxication. Ten days later the sedimentation rate (Wintrobe) was 15 mm., and the roentgenogram of the chest showed normal pulmonary markings and the same cardiac conditions as on admission.

CASE 4.—P. W., a 17 month old white girl, was admitted to the hospital Oct. 26, 1944. Eighteen hours before admission she had accidentally ingested approximately 1 teaspoonful of methyl salicylate. Five hours later she vomited, became restless and exhibited rapid respirations which persisted throughout the night. She continued to vomit the next morning and was brought to the hospital, where a diagnosis of salicylate intoxication was made.

On admission her temperature was 99 F., pulse rate 140 and respiratory rate 38. The child was lethargic and irritable when moved and vomited once, shortly after admission. The remainder of the physical examination revealed nothing significant, but roentgen examination of the chest revealed conditions consistent with bilateral bronchopneumonia. The carbon dioxide-combining power of the blood was 23 volumes per cent and the blood salicylate level 390 micrograms per cubic centimeter. The urine, which had a strong odor of wintergreen, contained a trace of albumin, gave a 1 plus reaction for acetone, and a 1 plus reaction for salicylates (Gerhardt's test) and contained no formed elements in the sediment.

The patient was given 5 per cent dextrose solution intravenously, and fluids were forced by gavage. She responded promptly to this treatment, and, since she was discharged on her second hospital day, no other laboratory studies were made.

COMMENT

The fatal result in the first case occurred because of lack of familiarity with the signs of salicylate intoxication,[5] our inability at the time to guide the daily dose of salicylate by the blood level attained the previous day and our unawareness of the possibility of salicylate intoxication in children on the dosage schedule and the desired blood salicylate levels outlined by Coburn.[1] He apparently did not encounter salicylate intoxication except in 1 of his patients, for he stated that "levels of 500 to 650 gamma can be produced by intravenous medication without causing disturbing symptoms," and that "the

4. Determined by a modified Quick procedure and calculated from the clotting times of 25 per cent plasma.

5. Barnett, H. L.; Powers, J. R.; Benward, J. H., and Hartman, A. J.: Salicylate Intoxication in Infants and Children, J. Pediat. **21**:214-223 (Aug.) 1942.

intravenous administration of sodium salicylate makes it possible to build up a plasma level of 400 or if necessary 650 gamma per cc. in a few hours and without causing symptoms other than mild tinnitus." Lacking the knowledge we now possess of the dangers inherent in this method of salicylate therapy when applied to children, we entered overenthusiastically on our treatment and continued it with a false sense of security.

That the dosages and blood levels recommended for young adults under Coburn's program cannot be followed safely in the treatment of children is evidenced by results for each of our 3 patients. These exhibited signs of salicylate intoxication while on the accepted dosage as outlined for young adults, i. e., 0.15 Gm. per kilogram of body weight. The intoxication of the first patient, receiving the drug intravenously, occurred early, after two days of treatment, with a blood level of 400 micrograms per cubic centimeter, which is considered within the range of the required therapeutic blood level (350 to 600 micrograms per cubic centimeter). Salicylism in the second patient developed after oral administration of the drug on the twenty-second day of treatment, with a blood level of 440 micrograms per cubic centimeter. The third patient was admitted with salicylate intoxication after four days of oral therapy with a blood level of 640 micrograms per cubic centimeter. The fourth patient, suffering from accidental salicylate poisoning with methyl salicylate, had on admission a blood level of salicylate (twenty-four hours after ingestion) of 390 micrograms per cubic centimeter.

It appears from the work of Lutwak-Mann [6] that deficiency of glycogen and of thiamine are likely factors in predisposing to sensitivity to salicylate. In children, acute or chronic illness with anorexia or vomiting leads to depletion of glycogen reserve and to vitamin deficiency as well as to disturbance in their unstable acid-base balance. Fashena [1c] has shown in her experimental cases that salicylate intoxication will occur easily in an acutely ill child and with more rapidity than in a well child. The latter may be given a dose of salicylate, 0.15 Gm. per kilogram per twenty-four hours, and at the end of twenty-four hours he may acquire the therapeutic blood level and maintain it for four days without signs of toxicity. Three of our patients were acutely ill with active rheumatic fever before the drug was given and unquestionably had disturbances of metabolic processes and possibly depletion of glycogen reserve. With these precepts in mi we treated our third patient with vitamin K combat the hypoprothrombinemia produced salicylates,[7] large doses of vitamin thiam hydrochloride to rectify any depletion, sodi lactate to correct the acidosis and a 10 per c dextrose solution to restore the glycogen reser

In our experience, it appeared that the d had a cumulative effect. In case 3, as dem strated by the blood levels, it was excreted slow In case 2, since the patient was treated under c trolled measures, it was necessary to adjust t dose frequently in order to maintain the desi therapeutic level; when this level was ma tained for twelve days, salicylate intoxication veloped and did not readily respond to reduction of the dose.

Although there was prompt clinical and sym tomatic relief of the polyarthritis in all our ca of rheumatic fever and disappearance of rheumatic nodules following salicylate thera in cases 1 and 2, beneficial results of the d on the rheumatic carditis appeared doubtful.

The unusual and unexplained nephrosis s in the sections of the kidneys of the first pati may explain the appearance in the urine o reducing substance, as well as of the protein a also the formed elements in the sediment in tients receiving salicylates.[8]

The conditions observed in the lungs of first patient at autopsy may explain the irregu consolidation in the upper lobe of the right lu the increased pulmonary markings and bronchopneumonia seen in the roentgenogra of the chest in cases 2, 3 and 4 during salicyl intoxication.

SUMMARY AND CONCLUSIONS

While we have not yet had sufficient exp ience with the type of case in which Cobur treatment was used, it nevertheless appears us that a longer period of observation is necessa before correct evaluation of this treatment can

6. Lutwak-Mann, C.: The Effect of Salicylate and Cinchophen on Enzyme and Metabolic Processes, Biochem. J. **36**:706-728 (Dec.) 1942.

7. Link, K. P.; Overman, R. S.; Sullivan, W. Huebner, C. F., and Scheel, L. D.: Studies on Hemorrhagic Sweet Clover Disease: XI. Hypop thrombinemia in the Rat Induced by Salicylic A J. Biol. Chem. **147**:463-474 (Feb.) 1943. Meyer, O. and Howard, B.: Production of Hypoprothrombine and Hypocoagulability of the Blood with Salicyla Proc. Soc. Exper. Biol. & Med. **53**:234-237 (Ju 1943. Shapiro, S.: Studies on Prothrombin: VI. Effect of Synthetic Vitamin K on the Prothrombi penia Induced by Salicylate in Man, J. A. M. A. **12** 546-548 (June 24) 1944.

8. Stevenson, C. S.: Oil of Wintergreen Poisoni Report of Three Cases, One with Autopsy, and Review of the Literature, Am. J. M. Sc. **193**:772-7 (June) 1937. Fashena and Walker.[2e]

tained. Salicylates when used in massive doses roduce toxic changes more readily in children an in adults,[2c] and before instituting this erapy one should be thoroughly familiar with e signs, symptoms and treatment of salicylate toxication. During treatment, the patient ould be hospitalized where adequate thera- utic and laboratory facilities are readily avail- le. The only definite clinical improvement seen our patients was the relief of the polyarthritis d the disappearance of the rheumatic nodules, result which can be obtained by smaller oral dosage. We have made no attempt to explain the metabolism or metabolic effects of the salicylates. The autopsy report included confirmed the fact that there is a tendency to bleed in severe salicylate intoxication and revealed the presence of changes in the lungs and kidneys which will bear further investigation.

Dr. B. B. Clark, department of physiology and pharmacology, Albany Medical College, performed the prothrombin studies, and Drs. Otto Faust and H. F. Leahy, department of pediatrics, gave permission to publish cases 2 and 3.

LARYNGEAL STRIDOR WITH TEMPORARY CARDIAC AND RESPIRATORY ARREST

A COMPLICATION OF THE OPERATION FOR CONGENITAL ESOPHAGEAL STENOSIS WITH TRACHEOESOPHAGEAL FISTULA

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The anomaly of congenital atresia of the esophagus with tracheoesophageal fistula has proved amenable to operation only in recent years. The postoperative complications of this procedure are not as yet completely understood. The following observations throw some light on an unusual and extremely serious postoperative syndrome. This consists of laryngeal stridor coming on during or shortly after a feeding. The stridor is often severe enough to cause cyanosis and on many occasions is accompanied with temporary cardiac and respiratory arrest. The patient whose case is reported has been previously mentioned by Haight,[1] but at the time of his report a full appreciation of the cause of the patient's symptoms and the appropriate therapy had not been reached.

REPORT OF A CASE

J. P. was admitted to University Hospital, Ann Arbor, Mich., on Sept. 9, 1943, weighing 5 pounds (2,268 Gm.) at the age of 4 days. Her referring physician, Dr. Thomas McEachern, had seen her for the first time on the day that she was admitted. He had obtained a history of choking at each attempted feeding of the infant, and it was his impression that the child had a tracheoesophageal fistula. He confirmed this impression by obtaining a roentgenogram with contrast medium in the esophagus which demonstrated an atresia of the esophagus at about the level of the second thoracic vertebra. Air was present in the stomach, which proved the existence of a fistula.

The infant was operated on by Dr. Cameron Haight on the day of admission. Anesthesia was induced by 0.25 per cent metycaine hydrochloride, administered locally, and by ether inhalation. The operation was performed through a parascapular incision on the right side, and the posterior portions of the third, fourth and fifth ribs were removed. Before the esophagus was exposed, the vagus nerve was blocked with a local anesthetic. When the esophagus was exposed, it was found that the two segments were adherent, the muscularis of the upper segment being in contact with a small portion of the muscularis of the extreme upper end of the lower segment. The level of contact was about 1.5 cm. abo the carina. The lower segment had a diameter of abo 6 mm. and the upper segment a diameter of about cm., which is not so broad as usual. A telescopic ty of anastomosis was done, and a good two layer clos was obtained. The closure of the trachea was airtig There was considerably less tension on the anastom sis than is usually the case. The patient's conditi throughout the operation was satisfactory, and operating time was two hours and forty minutes.[2]

During the first two postoperative days there w several periods of apnea and cyanosis, which w readily relieved by stimulants, artificial respiration a inhalations of oxygen and carbon dioxide. On the thi postoperative day, small feedings of dextrose w started orally, and, although respirations were no throughout feedings, no serious disturbances of res rations occurred. Starting on the twelfth postoperati day, this patient began to have increasingly severe e sodes of stridorous respirations coming on during shortly after feeding. These became severe enough cause cyanosis. On the forty-seventh postoperative d they were for the first time accompanied with cardi and respiratory arrest. This particular attack started usual, when after a feeding the infant began breathi noisily and appeared apprehensive. Breathing rapid became more difficult and stridorous, similar to th which occurs with acute laryngeal edema, and all t accessory muscles of respiration were brought into pl In a few minutes the infant became cyanotic, and su denly all respiratory attempts ceased in the expirato phase. She became limp, and no pulse was discernib It was thought that she had died, but, nevertheles strenuous attempts at resuscitation were carried o These included artificial respiration, inhalations of ox gen and carbon dioxide, pharyngeal suction and inj tions of nikethamide and caffeine. After about t minutes, during which there was no evidence of respi tory or cardiac activity, the infant vomited, passed loose stool and began breathing. At this time the pu was rapid and thready. Respirations were noisy a moist and continued so for about two hours. The pu rate rapidly returned to normal.

Similar severe episodes occurred six times in t month of November 1943 and nine times during D cember, six of the attacks taking place during the fi five days of December. They were accompanied w numerous less serious episodes of stridor and cyano following or during almost every feeding.

Owing to the severity of these attacks and th obvious connection with feeding, gavage feeding w instituted after the first week in December and w

From the Department of Pediatrics and Communicable Diseases, University Hospital.

1. Haight, C.: Congenital Atresia of the Esophagus with Tracheoesophageal Fistula, Ann. Surg. **120**:623-655, 1944.

2. The description of the operation is condensed fr the operative notes of Dr. Cameron Haight.

ontinued with only short trials of oral feeding until he middle of June 1944, eight and one-half months fter her operation. When gavage feeding was instituted, there was a considerable diminution in the number of severe attacks, but the lesser episodes of stridor ontinued. She was given a trial of atropine sulfate n the form of 1 drop of a 1:2,000 solution (approximately 0.00003 Gm.) ten minutes before each meal. Following the addition of this small dosage of atropine, here was a noticeable diminution in the number of esser episodes. These recurred when atropine was iscontinued three weeks later. Even when fed by avage, she continued to have occasional episodes of tridor with respiratory and cardiac arrest, but in general the situation was improving, so that from April o October 1944 she had only one severe episode a nonth. However, in November 1944, she had three, he last two of which occurred on November 25, during vhich she had complete respiratory and cardiac arrest or five minutes and three minutes respectively.

On November 29, after the patient had had two of er most severe episodes, administration of atropine vas again started. The dose of atropine was gradually increased to a point just below that which would ause an atropine flush. This was found to be 4 drops f the 1:2,000 solution four times daily (approximately .0005 Gm. per twenty-four hours). From the time he use of atropine was started until May 1945 (six nonths), she had no further severe attacks and only ccasional mild episodes of stridor. Atropine was discontinued on April 1. The patient continued to do well nd was discharged, apparently symptom free, on May , 1945.

COMMENT

When the described attacks first occurred, my ssociates and I assumed that an anatomic defect vas present, such as a leak at the site of anasomosis or a second fistula. Other congenital nomalies were considered, among them congenital laryngeal stridor. However, multiple oentgenologic examinations, both fluoroscopic nd roentgenographic with iodized poppyseed il in the esophagus, failed to reveal any evidence of a second fistula or a breakdown at the perative site. There was no evidence of obtruction and only slight narrowing at the site f anastomosis. Bronchoscopic and esophagoscopic examinations were performed, but no athologic condition could be observed, and the ite of the anastomosis could not be identified. Direct laryngoscopic examination proved the arynx and surrounding structures to be entirely ormal. The possibility that the cardiac slowing vas due to anoxia was also considered. This vas ruled out because of the rapidity with which he cardiac arrest developed following the onset f laryngeal stridor.

After many false leads we finally concluded hat the entire syndrome could well be explained as the result of excessive vagal stimulation. Cardiac inhibition, laryngeal spasm and respiratory arrest in expiration are well known vagal effects.

We were unable to obtain an electrocardiogram during an attack. Electrocardiograms made between attacks showed normal conditions. Pressure over the carotid sinus produced only slight temporary slowing of the heart. Pressure over each eyeball produced noticeable slowing with a short interval of cardiac standstill. This effect is not necessarily abnormal, since the same reactions were observed in 5 of 35 infants in the nursery at that time. We believe that normal vagal reflexes can be present without interfering in any way with abnormal vagal reflexes which may have developed.

We attempted to precipitate an attack by irritation of the pharynx, but were unable to do so. However, since every episode was so closely associated with eating, we have no doubt that eating in some way set off a chain of events that resulted in the laryngeal spasm and the cardiac and respiratory arrest. We did not attempt to inflate a balloon in the infant's esophagus. Furthermore, the attacks were so nearly fatal that we were much more anxious to avoid them than we were to precipitate them.

We felt that if our hypothesis was correct atropine was specifically indicated, owing to its blocking effect on structures innervated by postganglionic cholinergic nerves. Atropine was therefore administered in large doses, and the attacks ceased entirely. After four months of continuous administration, the use of atropine was discontinued. The severe attacks did not recur, but there was a recurrence of occasional mild episodes of stridor. We believe that the failure of the severe attacks to reappear means not that the atropine had no effect but rather that growth and development during the intervening four months had been sufficient either to diminish the response to the excessive vagal reflexes or to diminish the reflexes themselves.

Three cases with some features similar to those of this patient were described by Weiss and Ferris in 1934.[3] Their first patient was a man aged 64 who for ten years had suffered fainting spells precipitated by swallowing food. This was proved to be an Adams-Stokes syndrome with transient complete heart block. Roentgenologic studies revealed an anterior diverticulum in the lower third of the esophagus. Weiss and Ferris were able to precipitate the attacks by inflating a small rubber balloon in the esophagus

3. Weiss, S., and Ferris, E. B.: Adams-Stokes Syndrome with Transient Complete Heart Block of Vagovagal Reflex Origin, Arch. Int. Med. **54**:931-951 (Dec.) 1934.

at the level of the diverticulum. Electrocardiograms were not obtained during a spontaneous attack, but those obtained during a precipitated attack showed complete auriculoventricular dissociation. Those obtained between attacks were normal. The reflex nature of the syndrome was established by blocking the path of the sensory impulses. Following the injection of procaine hydrochloride into either of the vagal nerves, high in the neck, stimulation of the diverticulum failed to induce heart block. After the administration of atropine sulfate, 0.00054 Gm. three times a day, the patient was completely relieved of his symptoms.

Their second case was that of a housewife aged 59, who for ten days had had fainting spells precipitated by swallowing. An electrocardiogram taken during an attack showed prolonged irregular sinus pauses up to about four seconds. No partial or complete block was present. Spraying of the throat with cocaine prevented the attacks, which after the patient had spent two weeks in the hospital showed no tendency to return. A year later somewhat similar attacks occurred, which were relieved by tonsillectomy.

Their third case was that of a woman aged 28, who since the age of 2 had suffered frequent attacks of syncope associated with eating. An electrocardiogram showed partial and complete block when food was swallowed. Atropine completely abolished the attacks.

None of the patients reported on by Weiss and Ferris showed evidence of increased peristalsis, and none of them had laryngeal stridor with respiratory failure.

SUMMARY AND CONCLUSIONS

A syndrome following the operation for repair of congenital atresia of the esophagus with tracheoesophageal fistula is described. The syndrome consists of laryngeal stridor coming on during or shortly after feeding, followed by temporary respiratory and cardiac arrest and terminated by vomiting, the passage of a loose stool and the initiation of respiratory and cardiac activity. This syndrome is probably a result of excessive vagal activity, initiated reflexly through sensory endings in the pharynx. Cognizance of this syndrome and appropriate therapy has, I believe, been instrumental in prolonging the life of 1 patient and may be of importance in reducing the mortality which attends the operation for repair of congenital tracheoesophageal fistula.

Progress in Pediatrics

THE RHEUMATIC FEVER PROBLEM

I. PRESENT STATUS

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The introduction of the topic rheumatic fever to any group of clinicians initiates controversy. The reasons for this are apparent. The pathogenesis of rheumatic fever has been obscure, and the mechanism of the disease is still undetermined. Some of the problems awaiting solution have been defined at the bedside; however, their existence has not yet been fully grasped in the laboratory. And it is from the laboratory that clarification must stem. Until fundamental contributions are forthcoming, the clinical investigator has no alternative. He must develop a working hypothesis, test it, modify it and learn from it as much as possible. His concepts will therefore be based on personal observations. In this and in the following paper,[1] I shall attempt to explain my concept of rheumatic fever, with the hope that other workers will utilize their laboratory facilities for clarifying and solving the challenging problems of this important disease.

As physicians we are all impressed with the difficulties that arise in the accurate diagnosis of rheumatic fever. Until precise methods for diagnosis become available, we cannot expect general agreement on any aspect of this disease. However, I believe that we can begin by agreeing that probably no disease process is more unpredictable or has more vagaries than rheumatic fever. The unexpected is to be expected. Two rheumatic patients rarely manifest identical clinical syndromes, and two rheumatic attacks in the same patient are rarely similar. Furthermore, only a fraction of the activity of the rheumatic process is clinically detected. In one patient advanced rheumatic heart disease develops, which escapes detection until autopsy; another is found to have complete heart block without clinical symptoms of rheumatic fever. Moreover, symptoms and signs which appear to be classic manifestations of rheumatic fever may occur in other diseases. Migratory polyarthritis accompanies many diseases; mitral valvulitis occurs with disseminated lupus erythematosus; chorea is observed post partum; acute pericarditis and serofibrinous pleurisy are associated with the tuberculous state; the cutaneous lesions of rheumatic fever are indistinguishable from those observed with meningococcemia, periarteritis nodosa and serum sickness. In brief, no clinical manifestations are pathognomonic of rheumatic fever, and any disease process involving small blood vessels and serous linings may simulate rheumatic fever. The diagnosis of rheumatic fever is made by appraisal of clinical and laboratory observations. The accuracy of this appraisal depends on human intuitiveness, clinical acuity and critique developed from bedside experience.

At this time we must feel the lack of factual information on the pathogenesis of rheumatic fever. We can, nevertheless, show that the rheumatic attack evolves in an orderly manner. In these papers I shall attempt to point out the several phases that occur in this evolution and to indicate points at which the investigator can make contributions to the solution of the problem of rheumatic fever.

PATHOGENESIS

Factors in the Host.—At least three factors in the host play important roles in the evolution of the rheumatic state.

1. Heredity: The first of these is a constitutional factor, transmitted by the genes, probably as a mendelian recessive. This factor, it is believed, determines the metabolism of the host confronted with the problem of handling the products of streptococcic infection. So far as can be determined in a mixed metropolitan population, about 5 per cent of human subjects are constitutionally susceptible to the development of rheumatic fever. Maturation of the rheumatic process in this 5 per cent depends, however, on at least two other concomitant factors in the host.

Benjamin Knox Rachford Lecture delivered at Children's Hospital, University of Cincinnati, Cincinnati, Jan. 16, 1945.

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1. Coburn, A. F.: The Problem of Rheumatic Fever: II. Approaches Awaiting Development, Am. J. Dis. Child., this issue, p. 348.

2. Conditioning: The extraordinary inequality in distribution of rheumatic fever among the economic classes is a fact well recognized and widely investigated by students of rheumatic disease. It is well known that the disease has a higher incidence and is more severe in growing children than in mature adults. And there is general agreement that rheumatic fever is more common in cities than in country districts. British and Netherland observers have pointed out a striking difference in the severity of rheumatic disease between the children of Netherlands and those of England. Among the children of Netherlands there were only 228 deaths from rheumatic heart disease in the five year period from 1920 to 1925, whereas in England rheumatic fever was an important cause of death in childhood. Since there is no great difference in climate, race, age or incidence of infections of the respiratory tract affecting the children of these two countries, one must consider the possibility of a conditioning factor present in industrial urban populations and less common in rural communities. There is some evidence suggesting that this factor may be an inadequate diet.

3. Sensitization: A third factor which may be present in the host is an abnormal immune response of the rheumatic subject to the hemolytic streptococcus which results in sensitization. This peculiar response is associated with both genetic and with conditioning factors. The available data seem to indicate that the immune responses of the rheumatic subject differ from those of the normal subject in that they permit continued activity of the infectious agent and sensitization of the host. Development of sensitization in the rheumatic subject may occur in the following manner: (1) The immune response to a mild streptococcic infection of the upper respiratory tract is inadequate; (2) the inadequacy of the immune response results in continued elaboration of streptococcic antigens and sensitization of the reticuloendothelial system; (3) this sensitization is produced perhaps by a primary streptococcic antigen or, more likely, by a secondary antigen, which is a complex of substances from bacterium and host; (4) the induction of the sensitized state is followed by physiologic changes comparable to those characteristic of serum sickness; (5) the progressive elaboration of antigen tends to make the clinical reaction polycyclic.

Environmental Factors.—There may be many environmental factors which are conducive to the rheumatic state. However, the critical, precipitating factor is an infection of the respiratory tract with group A hemolytic streptococci. Despite the transient character of this infection, bacteriologic studies have repeatedly shown that the causative organism, the hemolytic streptococcus, may persist in the vicinity of the respiratory passages for months after its disappearance from the mucosal surface. The strains of hemolytic streptococci associated with the initiation of a rheumatic attack belong to Lancefield's group A and usually form matt or mucoid colonies on blood agar plates. They produce in vitro at least three soluble antigenic principles, erythrogenic toxin, fibrinolysin and streptolysin, and contain within the bacterial cell a number of other potential antigens, for example, nucleoproteins, type-specific M substance and group-specific carbohydrate. The liberation of streptococcic antigens in the infected host can be inferred from significant increases in specific antibodies. Most patients in the rheumatic state react negatively to the Dick test, indicating that they have produced neutralizing antibodies to the erythrogenic toxin. Increases in the antistreptolysin 0 and antifibrinolysin titers develop regularly during attacks of acute rheumatic fever. Most rheumatic patients show increased cutaneous reactivity to the nucleoprotein of hemolytic streptococcus. At the present time the available information does not permit an appraisal of the relative importance of these streptococcic products in the pathogenesis of rheumatic fever. However, it is known that erythrogenic toxin in patients with scarlet fever can damage the endothelium of the vascular tree. The action of nucleoprotein as an antigen after its liberation from the interior of the bacterial cell seems well established. Too little is known about the streptolysins or the M substance to permit an opinion on their immediate effects. Whatever the "rheumatic fever antigen" may eventually prove to be, it is definitely not associated with any serologic type of hemolytic streptococci but is a characteristic of the strain of Streptococcus.

Phases.—It is now well recognized that there are three phases in the development of a rheumatic attack.

Phase 1 (two to seven days): This phase is characterized as follows: (1) acute nasopharyngitis, of two to seven days' duration; (2) hemolytic streptococci present and frequently predominant in the flora of the throat; (3) temperature and pulse rate elevated to varying degrees; (4) electrocardiogram normal; (5) erythrocyte sedimentation rate moderately elevated; (6) antistreptolysin O titer normal or low.

Phase 2 (seven to twenty-one days, usually about fourteen): This phase is characterized as follows: (1) freedom from symptoms and signs of infection; (2) hemolytic streptococci predominant or present in the flora of the throat; (3) temperature and pulse rate normal; (4) electrocardiogram normal; (5) sedimentation rate fluctuating, returning to normal at end of period; (6) antistreptolysin 0 titer either increased or still within normal limits; (7) serum precipitinogen appearing late in this phase.

Phase 3 (first cycle of rheumatic attack, usually about three weeks): This phase is characterized as follows: (1) throat normal or infected; (2) many, few or no hemolytic streptococci in flora of throat; (3) abrupt onset of exudative manifestations of rheumatic fever; (4) temperature usually elevated, tachycardia common, bradycardia observed during heart block; (5) electrocardiogram showing prolongation of conduction time and other irregularities; (6) sedimentation rate rising rapidly prior to or with onset of symptoms; (7) antistreptolysin 0 titer rising at onset of attack and increasing progressively until after subsidence of symptoms; (8) other immune bodies to hemolytic streptococcus appearing during acute symptoms; (9) serum precipitin phase 2 precipitinogen appearing early in attack.

SEQUENTIAL DEVELOPMENT OF LESIONS OF RHEUMATIC FEVER

Both the clinician and the pathologist find it difficult to correlate the manifestations of rheumatic fever observed during life with the lesions seen at autopsy. For example, there seems to be no relation between chorea and a subcutaneous nodule or between a hemorrhagic consolidation of the lung and mitral valvulitis. Spindling of the phalangeal joints progressing to rheumatoid arthritis seems unrelated to acute pericarditis. There are good reasons for these difficulties: (*a*) Many manifestations of rheumatic fever, such as chorea, represent physiologic changes which cannot be studied in the microscope; (*b*) other rheumatic manifestations are evanescent, disappear early in the disease and are not detected post mortem; (*c*) opportunity to make histologic studies rarely occurs until the disease process has passed through its most acute stages, and (*d*) lack of a suitable experimental animal has made it impossible to study the sequential development of lesions of rheumatic fever under controlled conditions.

In cases of syphilis it is well recognized that a primary lesion is followed within a month by secondary lesions and that years elapse before the maturation of tertiary lesions. It is also well recognized that some of these tertiary lesions are free of spirochetal infection and that their pathogenesis is associated with the responses of the host to a preceding infection. It is also apparent that primary chancre, secondary rash and tertiary tabes dorsalis are caused by a single infectious agent but involve different disease mechanisms.

In the case of rheumatic fever, however, it is difficult to separate primary, secondary and tertiary lesions because the duration of each stage is relatively short, because most lesions are evanescent, because primary lesions may recur when tertiary lesions are far advanced and because there is much overlapping. In spite of many difficulties, one can attempt to chart the progress of a rheumatic attack and to classify the time relation of lesions.

It seems well established that the rheumatic attack may be monocyclic, polycyclic or continuous or may even merge into a rheumatoid state. Throughout the progress of rheumatic activity the state of the host appears to change. Lesions developing early appear to be associated with infection; lesions appearing weeks or months after the onset of an attack appear to be associated with disturbances in metabolism. The following analysis is presented to indicate time relations in the development of rheumatic phenomena:

Primary Lesion.—When the rheumatic process is activated, the primary biochemical lesion appears to occur in mucoprotein. Involvement of the cement substance of blood vessels results in changes in vascular permeability. The initial clinical response is characterized by manifestations of an exudative nature. Particularly common at this stage are hemorrhages, for example, epistaxis and the erythemas; melena, hemoptysis and hematemesis may also occur. Studies of the excretion of erythrocytes in the urine indicate the close relation of diapedesis of red blood cells to the activity of the rheumatic process.

When one studies the tissues of patients dying during the initial cycle of a rheumatic attack, hemorrhagic lesions without distinctive histologic structure are found to be conspicuous. The character of these nonspecific lesions suggests the activity of a single process with varying degrees of intensity: (1) engorgement of the blood vessels; (2) alteration in the permeability of the vascular tissues, with diapedesis of erythrocytes but without a demonstrable change in structure; (3) localized edema. During this, the first cycle of the rheumatic attack, few or no Aschoff bodies are detected in the cardiac

muscle; however, the presence of swollen collagen fibrils and edema of the subendothelial tissues of the mitral valve, giving rise to verrucae, establishes the diagnosis. These phenomena tend to be evanescent and reversible.

Secondary Lesion.—The early, evanescent physiologic changes in mesodermal tissues are followed by explosive reactions in endothelial and subendothelial cells. It appears that with these reactions there are liberated substances which are further damaging to tissues. Collagen fibrils undergo necrosis; vicinal heart muscle fibrils are fragmented, and fibrin and other serum constituents are deposited. These changes usually begin at the end of the first rheumatic cycle. They are followed by development of specific histologic lesions.

Tertiary Lesions.—Proliferative lesions occur weeks or months after the onset of exudative phenomena. In fact, the subcutaneous nodule may not appear until the rheumatic process appears to have become quiescent. The pathogenesis of these late manifestations is obscure. It may well be that the biologic or biochemical systems involved in the pathogenesis of these late reactions are secondary to but different from those concerned with the initiation of primary lesions.

Sequelae.—Even more obscure is the pathogenesis of certain sequelae, such as rheumatoid arthritis. Tissues which have previously undergone reversible changes early in a rheumatic attack appear to become involved in a progressive disease process, which is not readily reversed.

There are also striking differences in the reactivity of the rheumatic patient during the progress of disease activity. Whereas the primary manifestations are closely associated with increasing titers of streptococcic antibodies, the late manifestations may occur in the absence of clinical, bacteriologic or serologic evidences of streptococcic activity. Although the rheumatic process is initiated by infection with the hemolytic streptococcus, recurrences during convalescences may be precipitated by many nonspecific factors. For example, it has been observed that severe, and even fatal, exacerbations of rheumatic fever may be precipitated by (*a*) active immunization with bacterial proteins or horse serum, (*b*) severe sunburn, (*c*) fracture of long bones, (*d*) tonsillectomy, (*e*) tooth extraction or (*f*) splenectomy. In contrast to the rheumatic cycle, which occurs about ten days after the patient's recovery from streptococcic infection, these exacerbations develop promptly, within a few hours after stimulation of the reticuloendothelial system. The simplest explanation offered for these exacerbations is that in the course of a rheumatic attack the patient becomes sensitized but that this sensitization may not be confined to a product of the hemolytic streptococcus. In fact, the rheumatic patient may be refractory to a superimposed hemolytic streptococcus infection of the throat and yet may manifest a violent reaction within a few minutes after nonspecific stimulation of the reticuloendothelial system.

The genesis of tertiary lesions appears to be dependent on progressive rheumatic activity. Whether there is a mechanism common to both early and late rheumatic manifestations or whether the damage to the tissue incurred in primary lesions gives rise to a secondary mechanism, such as an auto-antigen-antibody reaction, is unknown. It is of interest, however, that the genesis of rheumatoid arthritis as a sequel of rheumatic fever is accompanied with the appearance of a peculiar substance in the circulation. This substance is an agglutinin for the hemolytic streptococcus; however, its presence appears to be independent of streptococcic activity. Whether this agglutinin is an autoantibody and whether the rheumatic subject may become sensitized to a human protein are problems awaiting solution by the immunologist. It is common experience, however, that the therapeutic agents which are effective in modifying primary lesions are ineffective in modifying tertiary lesions.

PROBLEM OF RHEUMATIC FEVER IN THE UNITED STATES NAVY

Essential both to an understanding of the problem of rheumatic fever and to the care of the rheumatic subject is a full appreciation of the close association between hemolytic streptococcus infection of the upper respiratory tract and activation of the rheumatic process. This relationship is especially striking in naval recruits among whom rheumatic fever is prone to occur in explosive outbreaks following seasonal epidemics of streptococcic infections. These explosive outbreaks show the same sequence of events that is observed in civilian practice and present problems in the care of large numbers of rheumatic patients with a great variety of manifestations. For these reasons, it may be advantageous to examine some of the problems connected with rheumatic fever that arise in the United States Navy and to outline the control measures that are being employed

Morbidity rates for scarlet fever reached an all-time high for the United States Navy in 1943. In certain areas, climatically conducive to streptococcic infections, morbidity rates among Naval recruits have been 100 to 500 per cent higher than the rates among the civilian population. The high incidence of streptococcic diseases in Naval training camps is probably due to many factors: (*a*) the susceptibility of young recruits, (*b*) the lowered resistance associated with the rigors of training and with active immunizations, (*c*) the rapidly changing population, (*d*) the prevalence of virus infections of the respiratory tract, (*e*) the seeding of convalescent carriers of hemolytic streptococci in barracks with newly arrived recruits and (*f*) the introduction of highly communicable strains of the hemolytic streptococcus. Other conditions, difficult to evaluate, have also played important roles in the pathogenesis of streptococcic infections at Navy recruit camps. Cleaning the floors of barracks, dispensaries and hospitals with steel wool and dry sweeping, procedures common to all naval training activities, disseminated contaminated particles of dust and blanket lint among the men congregated there. Unfavorable climatic conditions and little sunlight during the winter months resulted in congestion of men indoors at the stations with the highest morbidity rates. Still other factors may have been (*a*) high temperature and low humidity in barracks, (*b*) assignment of new recruits to barracks already contaminated by companies which were graduating, (*c*) employment of double deck or triple deck bunks and (*d*) overcrowding of sick bays, dispensaries and hospitals during the winter months. These conditions facilitated (*a*) lowering of resistance of the mucous membranes of the respiratory tract; (*b*) indirect transmission of air-borne pathogens of the respiratory tract in dispensaries, hospitals and sleeping quarters; (*c*) direct transfer of these agents from infected persons or convalescent carriers to "shipmates," and (*d*) progressive increase in virulence of the prevalent strains of the hemolytic streptococcus.

Wherever streptococcic infections have become prevalent in recruit camps, the Navy has been confronted with the problem of rheumatic fever. In 1943 nearly 5,000 members of the Navy personnel had initial attacks of rheumatic fever, and others had recurrences. The recruits who had rheumatic fever may be divided into three groups: (*a*) those with rheumatic heart disease whose lesions escaped detection on the initial physical examination, (*b*) those who, in their patriotic enthusiasm, denied having had a previous rheumatic attack and (*c*) who were susceptible but had escaped exposure to hemolytic streptococcus infections in their home environment. Since a large percentage of the Navy's recruits is comprised of men in their second decade who come from areas where exposure to streptococcic infection is minimal, it is not surprising that most patients have fallen into group *c*. Exposure to infection and incidence of rheumatic fever have been generally lower among groups undergoing advanced training. The lowest morbidity rates for rheumatic fever in the Navy have been found among men afloat or ashore outside the continental limits of the United States in areas where there is minimal exposure to streptococcic disease of the respiratory tract.

The distribution of rheumatic fever in Naval recruit camps has paralleled the distribution of scarlet fever. Naval activities situated in northern states have had a relatively high incidence of both diseases, and those in southern states have had a relatively low incidence of both diseases. The highest morbidity rates for both scarlet fever and rheumatic fever have occurred in the Northwest, in the Rocky Mountains. These observations are shown in table 1.

TABLE 1.—*Morbidity Rates for 1943 (Annual Rate per Thousand) at United States Naval Training Centers*

	Average for 6 Months	
	Scarlet Fever	Rheumatic Fever
Idaho	111.03	18.77
Illinois	11.28	5.51
New York	3.25	1.03
Rhode Island	1.30	2.72
Virginia	0.81	0.61
Maryland	0.56	0.96
California *	1.37	1.34

* In this table, and in table 2, the morbidity rates for scarlet fever and, especially, for rheumatic fever at this activity are in part due to newly arrived trainees, who were infected at a naval activity in Idaho.

A sharp decline in the morbidity rates for scarlet fever and rheumatic fever has been observed each summer at all Naval activities, with one exception. In this training center, located in the Rocky Mountains of Idaho, the hemolytic streptococcus maintained its pathogenicity throughout the summer months. The morbidity rates for both scarlet fever and rheumatic fever were maintained at high levels. This is shown in table 2.

The Use of Chemoprophylaxis for Rheumatic Fever in the United States Navy.—Continuous prophylaxis with sulfadiazine, 1 Gm. daily, was administered to large numbers of Naval recruits in 1943 and 1944. The purpose of this control measure was to prevent implantation of hemolytic streptococci in the flora of the throats of susceptible recruits at Naval activities where strep-

tococcic infections were prevalent. An analysis of the data collected over a period of six months showed that this measure was approximately 85 per cent effective in preventing streptococcic infections of the upper respiratory tract.

The reduction in rheumatic fever which followed the institution of chemoprophylaxis was comparable to that observed for tonsillitis and scarlet fever except that in most instances the effect of chemoprophylaxis was not observed during the first ten days. The reduction began in the second week and was progressive. Chart 1, *A*, *B* and *C*, shows observations made at three Naval activities.

Chart 1 *A* illustrates the slowly progressive fall in the morbidity of rheumatic fever at a station experiencing an epidemic of streptococcic infection. One half of the recruits of this station of 16,000 men received chemoprophylaxis.

rheumatic fever in each group were contracte prior to entry of the men into recruit training and rheumatic attacks in these instances wer not preventable by chemoprophylaxis. Chart 1 shows the incidence of rheumatic fever prior t and during chemoprophylaxis in a station o 10,000 men. This station was experiencing severe epidemic of streptococcic infection, an a high incidence of rheumatic fever was to b expected in March and April. Chemoproph laxis was given to all the men on Feb. 8, 194 A sharp drop in the morbidity rate of rheumati fever occurred two weeks later, and this wa progressive until April, when the weekly mor bidity rate fell to zero, where it remained.

Treatment of Rheumatic Fever in the Unit States Navy.—Each rheumatic patient presen an individual problem, which tests the Nav medical officer's understanding of the rheumati

TABLE 2.—*Morbidity Rates (Annual Rate per Thousand) During the Summer and Fall Months of 1943*

	Scarlet Fever						Rheumatic Fever					
	June	July	Aug.	Sept.	Oct.	Nov.	June	July	Aug.	Sept.	Oct.	Nov.
Idaho	85.43	69.25	88.17	125.72	150.35	147.23	13.10	13.42	7.47	17.28	25.06	36.27
Illinois	34.63	3.57	0.15	0.45	4.08	24.82	14.92	7.47	2.61	3.31	3.93	0.89
New York	11.41	3.47	0	0	1.35	3.27	1.34	1.58	1.94	0.34	0.67	0.33
Rhode Island	2.46	0.56	0.55	0	1.76	2.46	7.99	1.12	3.86	1.14	0.59	1.64
Virginia	1.05	0	0	0.85	0	2.98	2.11	0	0	0	1.55	0
Maryland	1.07	1.06	0	0	0.80	0.42	0.49	1.06	0.52	0	0	3.78
California	1.92	0	0	0.89	0	5.42	0.96	0.91	1.65	0.44	1.36	2.71

Chart 1 *B* shows the effect of sulfadiazine administered to 30,000 men in recruit camps on the incidence of rheumatic fever. These men,

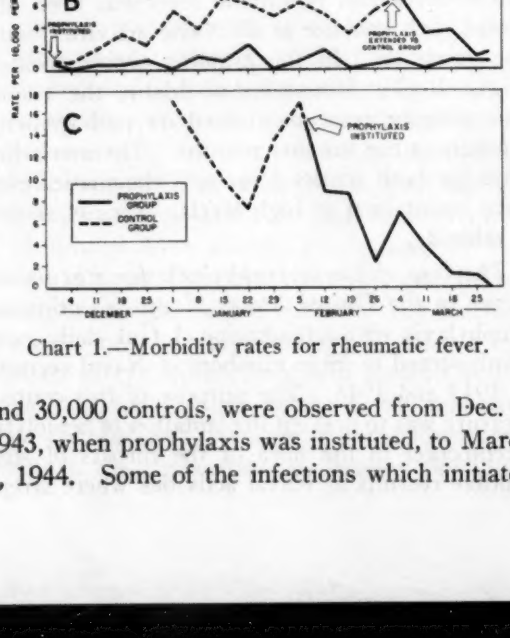

Chart 1.—Morbidity rates for rheumatic fever.

and 30,000 controls, were observed from Dec. 1, 1943, when prophylaxis was instituted, to March 1, 1944. Some of the infections which initiated

process and his therapeutic skill in handling great variety of clinical manifestations. Funda mental to this understanding must be a clea conception of the close association between th initiation of rheumatic activity and hemolyt streptococcus infection of the upper respirator tract. It is my opinion that this association i as close as inhalation of ragweed pollen and th reaction to this antigen of a person subject t hay fever. Hay fever is initiated by the protei of a plant; rheumatic fever, by some produc of the group A hemolytic streptococcus. Bot occur when the appropriate antigen is prevalen and both occur only among constitutionally sus ceptible subjects. When ragweed pollen disap pears from the air the person subject to ha fever may lead a normal life, and when strepto coccic activity subsides the rheumatic subjec may also regain the ability to live naturally. On striking difference, however, is the time require for the return of the predisease capacity fo work. In the person subject to hay fever, th involved tissues of the respiratory tract recove rapidly with subsidence of the disease activity in the rheumatic subject tertiary lesions mus be repaired. And in the muscle of the heart, on which the body's demands for work are exacting

the processes of repair are slow. It is for this reason that great care must be given the rheumatic patient not only during his illness but throughout convalescence and into recovery. Without this care the patient may be handicapped by a poor myocardium and become a future liability to himself, as well as to the Navy.

The strategy used by the Navy in the treatment of rheumatic fever was designed for a single purpose, to prevent disabling heart disease. The measures employed were as follows:

1. Hospitalization at the onset of the rheumatic attack.

2. Treatment with salicylate in a dosage adequate to cause a rapidly progressive decline in the blood sedimentation rate to normal.

3. Early transfer of the patient by air ambulance from the environment in which the disease was contracted to an isolated environment in Southern California.

4. Exposure of the patient to increasing amounts of sunlight.

5. Slowly progressive increases in physical activity after quiescence of the rheumatic process is established.

To effect this plan a rheumatic fever hospital was established at Corona, Calif. The management of rheumatic patients was synchronized with the progress of the disease process. To facilitate this, the treatment of the rheumatic attack was divided arbitrarily into four periods.

Stage 1: This was the period of acute illness, during which the patient was believed subject to multiple inflammatory reactions. It was felt that the extent of the myocardial damage would depend on the number and location of these lesions in the heart. During the acute illness it was advised that each rheumatic patient be treated at a Naval hospital with maximum rest in bed and sodium salicylate. Unless there were contraindications, administration of 1.6 Gm. of sodium salicylate with 0.6 Gm. of sodium bicarbonate every four hours, day and night, was advised. This stage in most instances was completed within one month. At this time patients who were free from symptoms, who had a normal blood sedimentation rate and whose hearts were compensated were transferred, preferably by air transport, to a rheumatic fever hospital, at the discretion of their commanding officer.

Stage 2: On his arrival at the Rheumatic Fever Hospital, the patient was considered subacutely ill. During this subacute stage of the disease it was advised that he be given rest in bed and maintained on sodium salicylate (10 Gm.) and sodium bicarbonate (4 Gm.) daily until the blood sedimentation rate proved to be normal for two weeks. After the blood sedimentation rate had been normal for two weeks, salicylate therapy was discontinued abruptly. If one week later the patient was still free from symptoms and signs of rheumatic activity and the blood sedimentation rate was normal, he was considered to have progressed to stage 3.

Stage 3: Stage 3 was considered a period of healing. Although the inflammatory process had subsided, recently damaged tissues had to be repaired. The process of repair in the heart muscle is recognized to be slow. To effect maximal repair with minimal loss of time, it was therefore essential that no great strain be placed on the myocardium during this period. A slowly progressive increase in physical activity was advised. If, after four weeks, the patient manifested ability to carry on light physical activities without tachycardia or other symptoms and maintained a normal blood sedimentation rate, he was considered to have progressed to stage 4.

Stage 4: At this point it was believed that the patient was free from active disease and that the cardiac lesions, which developed during stage 1, had healed. Every effort was made during this stage to prepare the patient physically for return to duty. At the end of this stage he was found capable of performing all work consistent with his blood sedimentation rate.

Disposition: At the appropriate time each patient's status was reviewed by a Board of Medical Survey. One of three recommendations was made at this time. It the patient had escaped all evidence of heart disease, it was recommended "that he return to duty, fit for same." If the patient had stigmas of heart disease but had, nevertheless, progressed satisfactorily in stage 4, it was recommended "that this man return to duty and be placed within the 6th, 7th, 10th, 11th or 15th Naval District [2] because of proved susceptibility to rheumatic fever." If the patient had manifested incapacitating heart disease and had been unable to advance beyond stage 3 after six months of convalescence, it was assumed that his myocardial damage had been severe enough to preclude further Naval service, and it was, therefore, recommended "that he be discharged from the United States Navy."

This plan for handling rheumatic patients is summarized in chart 2. The results during the first eight months have been analyzed. Approximately 5,600 rheumatic patients were treated

2. These Naval Districts have a tropical or a semitropical climate.

between March and December 1944 at Naval hospitals in southern California. To date, over 80 per cent of these men have been returned to duty. Less than 3 per cent have subsequently been readmitted to the sick list. The factors which led to progressive heart disease in a small percentage of patients have not yet been analyzed. Five patients in this series died. The deaths of 3 of these patients were attributable to errors in judgment of the patient's ability to travel in an ambulatory status. One resulted from a coronary occlusion following tonsillectomy. One patient's was attributable to his treatment while in convalescent status.

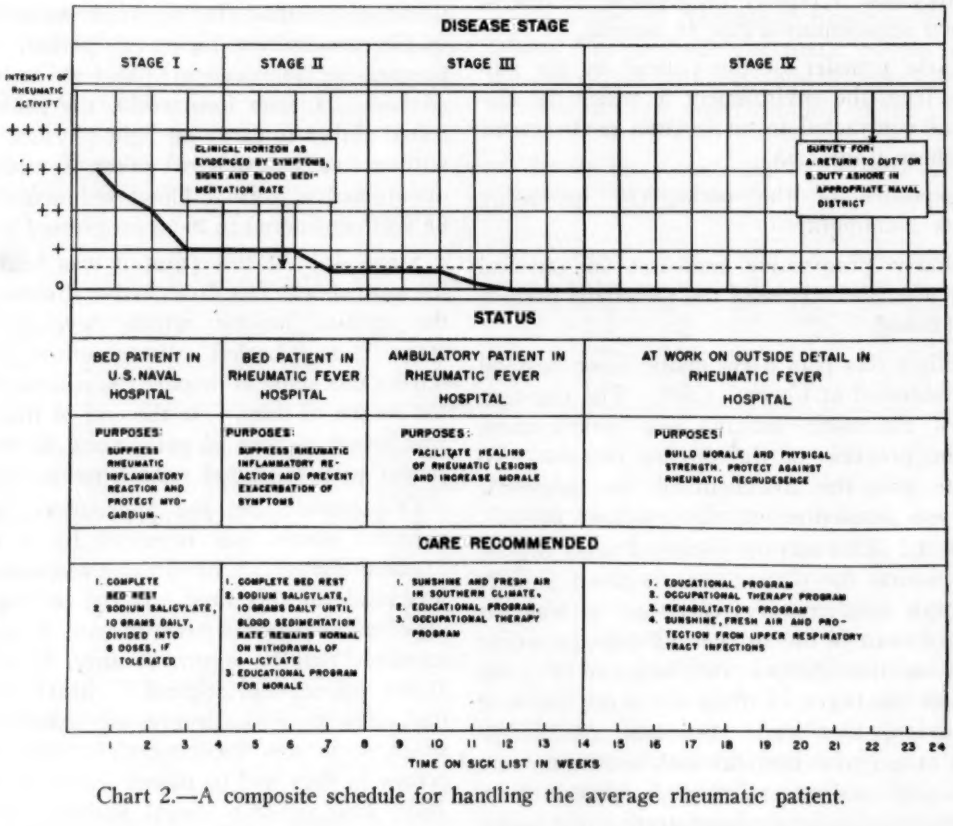
DISEASE STAGE
STAGE I
STAGE II
STAGE III
STAGE IV
INTENSITY OF RHEUMATIC ACTIVITY
++++
+++
++
+
0
CLINICAL HORIZON AS EVIDENCED BY SYMPTOMS, SIGNS AND BLOOD SEDIMENTATION RATE
SURVEY FOR: A. RETURN TO DUTY OR B. DUTY ASHORE IN APPROPRIATE NAVAL DISTRICT
STATUS
BED PATIENT IN U.S. NAVAL HOSPITAL
BED PATIENT IN RHEUMATIC FEVER HOSPITAL
AMBULATORY PATIENT IN RHEUMATIC FEVER HOSPITAL
AT WORK ON OUTSIDE DETAIL IN RHEUMATIC FEVER HOSPITAL
PURPOSES:
SUPPRESS RHEUMATIC INFLAMMATORY REACTION AND PROTECT MYOCARDIUM.
PURPOSES:
SUPPRESS RHEUMATIC INFLAMMATORY REACTION AND PREVENT EXACERBATION OF SYMPTOMS
PURPOSES:
FACILITATE HEALING OF RHEUMATIC LESIONS AND INCREASE MORALE
PURPOSES:
BUILD MORALE AND PHYSICAL STRENGTH. PROTECT AGAINST RHEUMATIC RECRUDESENCE
CARE RECOMMENDED
1. COMPLETE BED REST
2. SODIUM SALICYLATE, 10 GRAMS DAILY, DIVIDED INTO 6 DOSES, IF TOLERATED
1. COMPLETE BED REST
2. SODIUM SALICYLATE, 10 GRAMS DAILY UNTIL BLOOD SEDIMENTATION RATE REMAINS NORMAL ON WITHDRAWAL OF SALICYLATE
3. EDUCATIONAL PROGRAM FOR MORALE
1. SUNSHINE AND FRESH AIR IN SOUTHERN CLIMATE.
2. EDUCATIONAL PROGRAM.
3. OCCUPATIONAL THERAPY PROGRAM
1. EDUCATIONAL PROGRAM
2. OCCUPATIONAL THERAPY PROGRAM
3. REHABILITATION PROGRAM
4. SUNSHINE, FRESH AIR AND PROTECTION FROM UPPER RESPIRATORY TRACT INFECTIONS
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
TIME ON SICK LIST IN WEEKS

Chart 2.—A composite schedule for handling the average rheumatic patient.

MEASURES FOR PREVENTION OF RHEUMATIC HEART DISEASE

The application of any measure for preventing the initiation or perpetuation of rheumatic heart disease must be determined by the phase of the rheumatic state in which the patient presents himself.

So long as the rheumatic state is quiescent, the problem of prophylaxis is well defined. Hemolytic streptococcus infection of the upper respiratory tract must be prevented. This can be effected in either of two ways: (*a*) by minimizing exposure to hemolytic streptococcus infection through change in geographic environment or (*b*) by preventing implantation of hemolytic streptococci in the mucous membranes of the nasopharynx through chemoprophylaxis.

The initiation of phase 1 with an acute hemolytic streptococcus infection of the upper respiratory tract releases a trigger mechanism. Chemotherapeutic agents are theoretically useless in this phase, and clinical observations have indicated that they are ineffective. In fact, no preventive measure can at present be visualized which if applied only in phase 1, when the rheumatic mechanism is initiated, will prove effective.

The application of preventive measures in phase 2 depends on the recognition of phase 1. There is evidence that administration of sodium salicylate for fourteen to twenty-one days after a streptococcic infection of the throat prevents or modifies the development of a rheumatic attack. It is reasonable to expect the development of other effective preventive measures during this phase.

Phase 3 is difficult to control. When the rheumatic attack becomes manifest, damage to the tissues has occurred. The essential problem in the management of phase 3 is the prevention of disabling heart disease. One can treat the patient symptomatically and allow the disease to run its natural course. An alternative is to

attempt to suppress the intensity of the rheumatic process as early as possible in the attack.

If the rheumatic attack were always monocyclic, severe damage to the heart muscle would rarely occur. However, in children and young adults rheumatic fever is more commonly polycyclic, and during each febrile phase of the cycle severe inflammatory reactions take place in vascular tissues. These reactions continue to occur so long as the pathogen of the respiratory tract (hemolytic streptococcus group A) liberates antigen and induces an abnormal antibody response in the rheumatic subject. Since there are no methods available either for suppressing the elaboration of antigen by the bacterial agent or for modifying the constitutional defect of the host, effective handling of the rheumatic patient must depend, for the present at least, on complete utilization of all available therapeutic instruments. The objective in the treatment of each patient must be to reduce cardiac damage to a minimum, and to effect this it is essential that the inflammatory reaction of rheumatic fever be suppressed.

Recent studies made in the Navy on a small number of young adults suggest that induction of a plasma salicylate level of 35 mg. per hundred cubic centimeters at the onset of a rheumatic attack may exert a suppressive effect. In these studies the objective was to restore the blood sedimentation rate to normal as rapidly as possible. In a few patients with extremely high sedimentation rates higher plasma levels were required to reverse the sedimentation rate. In most patients admitted to the hospital during the first week of rheumatic attack with sedimentation rates of 100 mm. in one hour (Westergren) it was possible to attain the desired objective. The induction of a plasma salicylate level of 35 mg. per hundred cubic centimeters at the onset of the attack and the maintenance of this level until the disease process subsided appeared to minimize injury to tissue by the rheumatic process. Even though salicylate may prove to have a prophylactic effect early in the rheumatic process, it does not appear to modify a tertiary lesion, such as the Aschoff body or the subcutaneous nodule, or a sequela, such as rheumatoid arthritis, and it does not aid in the healing of tissues which have been injured. Other measures must be conceived to interrupt the vicious chain of events which occur late in the rheumatic attack. The treatment of tertiary rheumatic manifestations poses a problem in altering a mechanism induced originally by infection but perhaps not dependent on persistent activity of an infectious agent.

Salicylic acid is not the final solution to the therapeutic problems arising in rheumatic fever. With the development of methods of determining the level in the blood, other drugs may be found more effective in suppressing the rheumatic reaction, but, like salicylic acid, these will probably not modify the duration of rheumatic activity. To effect this, one of two objectives must be realized. Either the biologic response of the host must be modified so that the patient recovers promptly after a monocyclic attack, or the capacity of the infecting micro-organism to elaborate antigen must be inhibited by a chemotherapeutic agent. Since neither of these objectives has yet been realized, one is limited to the suppression of the inflammatory process. For this purpose, a high concentration of salicylate in the plasma appears to be effective if attained during the first cycle of the rheumatic attack and maintained until the rheumatic process becomes quiescent.

SUMMARY

This description of the present status of the problem of rheumatic fever is drawn from the personal experiences of one observer. Many of the concepts suggested for consideration are controversial topics. The present working hypotheses offer an opportunity to apply measures for the prevention of rheumatic heart disease. Future progress in the solution of the problem of rheumatic fever awaits fundamental research on the mechanism of this disease and clinical investigation of possible control measures. Some of the approaches to this problem will be discussed in a subsequent paper.[1]

THE RHEUMATIC FEVER PROBLEM

II. APPROACHES AWAITING DEVELOPMENT

CAPTAIN ALVIN F. COBURN (MC), U.S.N.R.

The clinician sees disease problems as they are presented by Nature. He has access to the knowledge accumulated in medical books and to recent experimental findings recorded in scientific papers. It is, nevertheless, difficult for the clinician to correlate the findings of the laboratory with his observations at the bedside, and yet progress depends on his defining for the investigator the clinical problems awaiting solution. The solution of important disease problems requires that the man who works in the "field" with Nature's phenomena have a close liaison with the man who by his training in fundamental sciences is equipped to direct laboratory methods. This is especially true in the study of rheumatic fever, and it is in the role of liaison between clinician and investigator that I should like to present this lecture. The material to be presented will be highly speculative. It will include possible attacks on the problem of rheumatic fever and will be based on the concepts discussed in the first lecture of this series. But before indicating some of the possibilities for research on the rheumatic state, I want to review briefly the ideas, discussed in the first lecture of this series, on the 3 phases in the genesis of rheumatic heart disease.

PHASES OF RHEUMATIC HEART DISEASE

Phase 1.—The hemolytic streptococcus infection which precipitates rheumatic fever is usually mild and nonsuppurative and is followed by prompt clinical recovery. The infecting strain may be of any serologic type. However, in an epidemic of nasopharyngeal infections some strains of one type may precipitate a high incidence of rheumatic fever, whereas in a comparable epidemic other strains of the same serologic type may precipitate little or no rheumatic fever. The capacity of the micro-organism to induce rheumatic fever appears to be a strain characteristic and is not limited to any serologic type but does appear to be limited to group A hemolytic streptococci.

Phase 2.—It appears that the human host passes through an immunologic crisis between one and three weeks after recovery from a streptococcic infection. In nonrheumatic subjects, this phase is usually passed without detectable manifestations of disease. One possible exception is microscopic hematuria, which occurs regularly at the time of this crisis and which in rare instances reaches the intensity of acute hemorrhagic nephritis. In rheumatic subjects this crisis is commonly accompanied with the onset of an acute rheumatic attack. The intensity of the reaction which may occur during this crisis is unpredictable. The trigger mechanism when released may induce biochemical changes so severe that they lead to fulminating disease, so subtle that they lead to an insidious rheumatic attack or so mild that they produce only the microscopic hematuria characteristic of the normal reaction.

The mechanism of rheumatic fever is not known. The following hypothesis is presented as a possible explanation. During hemolytic streptococcus nasopharyngitis, erythrogenic toxin or some other streptococcus product or constituent attacks endothelium. During phase 2 this bacterial substance is conjugated with human material and forms a complex. This antigenic complex may consist of a protein and a hapten of which one is bacterial and the other human in origin. The complex acts as a secondary antigen in phase 2 and induces the formation of a secondary antibody in phase 3. This secondary antibody reacts not only with the circulating secondary antigen but also with the antigenic component in endothelial tissues. The intensity of the reaction is determined by the concentration of secondary antibody, and the site of the reaction is determined by the localization of the antigenic complex or constituent with which the antibody reacts specifically. This interaction gives rise to the biochemical changes which characterize rheumatic activity.

Benjamin Knox Rachford Lecture, delivered at Children's Hospital, University of Cincinnati, Cincinnati, Jan. 17, 1945.

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The opinions and views set forth are those of the writer and are not to be construed as reflecting the policies of the Navy Department.

Phase 3.—The mechanism released in phase 3 is self limited. The intensity of its reaction usually reaches a peak within ten to fourteen days and then subsides rapidly. The rheumatic attack, like most attacks of serum sickness, can be monocyclic. However, unlike that in most cases of serum sickness, the rheumatic mechanism is commonly repetitive, with several cycles of disease recurring about one week after the subsidence of symptoms. Areas of the body which may have escaped injury in the first cycle are commonly involved during subsequent cycles. The cutaneous manifestations are usually bilateral and symmetric. The localization of these lesions seems to be associated with nerve distribution. The progressive rise in streptococcus antibodies during polycylic attacks indicates that there occurs a continued elaboration of streptococcus antigens and suggests that this is essential to the rheumatic mechanism. However, there is the added possibility that resensitization may depend also on the splitting of the sensitizing complex formed in phase 2. The relative importance of primary and secondary antigens in the progressive development of rheumatic heart disease has not been determined.

Before planning research on rheumatic fever, the investigator must bring into clear focus the state of the rheumatic subject. Each phase of the disease presents its own problems. These problems must be considered individually if rational designs for prophylaxis and treatment are to be effected. For example, one may begin during the prerheumatic state by attempting to prevent streptococcic infections of the throat or by attempting to control the conditioning factors which increase rheumatic susceptibility. One may also introduce prophylactic measures during phases 1 and 2 to suppress the maturation of the rheumatic process. Early in phase 3 one may initiate therapeutic measures to minimize the intensity of the rheumatic reaction.

Late in phase 3 the therapeutic problem may be complicated by progressive changes in the biologic responses of the host. Immunochemists have shown that after successive courses of immunization one can expect in the experimental animal the formation of more and more antibody, capable of reacting with a larger number of chemically different groupings on the antigen molecule. Furthermore, it has been demonstrated that under these experimental conditions a proportion of the antibody molecules varies sufficiently to permit specific union with heterologous antigens. Just what role such nonspecific antibodies may play in disease mechanisms and how they affect sensitized tissues remain to be determined by future studies in cell physiology. It is possible that the failure of salicylates to be effective late in phase 3 may be associated with the presence of antibody molecules which react irreversibly with tissues of the rheumatic patient. This presents an interesting point for investigation.

There are also rich fields for research in the development of technics for exact diagnosis, for modification of the immune reactions and for alteration of susceptibilty of the host to the rheumatic reaction. It is these problems and the possibilities for attacking them with methods now available that I wish to discuss.

I. PREVENTION OF STREPTOCOCCIC INFECTIONS

The investigator of rheumatic fever is now justified in believing that the initiation of rheumatic activity depends on infection with group A hemolytic streptococci. If the rheumatic subject escapes streptococcic infection of the upper respiratory tract, he escapes rheumatic fever. The first problem in the control of rheumatic fever is, therefore, the prevention of streptococcic nasopharyngitis. There are at least three approaches to this problem: (A) placing of the rheumatic subject in an environment which is unfavorable to the occurrence of streptococcic infections of the respiratory tract, (B) modification of the secretions of the nasopharynx so that implantation of hemolytic streptococci is prevented and (C) inhibition of communicable strains of hemolytic streptococci.

A. *The Utilization of Favorable Environmental Factors.*—There is evidence that rheumatic fever rarely occurs in certain geographic locations. These environments are areas where there are minimal fluctuation in temperature and maximum hours of sunlight. To date, the perfect geographic environment has not been defined. This is because it is not known whether climatic factors (*a*) favor the establishment of bacteria in the throat flora which are antagonistic to the implantation of hemolytic streptococci, (*b*) inhibit the activity of hemolytic streptococci or (*c*) modify the reactivity of the host. These problems need to be investigated. The discovery of an inhibitory bacterium indigenous to the throat flora of persons living in the tropics has obvious practical implications. Furthermore, if antigen [1] formation is controlled by intracellular

1. It has been repeatedly observed that during September and October it is difficult to type serologically the strains of group A hemolytic streptococci recovered from the throat flora of persons in New York City. In several carriers, the persistent strain was typable during the spring months, became untypable in the summer and was again typable during the winter. Ob-

(Footnote continued on next page)

enzymes of the bacterium and if these enzymes are modified by the effects of temperature and sunlight, it should be possible to demonstrate these relationships. The acquisition of this knowledge can be applied in those geographic areas where the environment is favorable to full activity of hemolytic streptococci. Moreover, if it be shown that sunlight modifies the reactivity of the rheumatic subject to hemolytic streptococci, it should be possible to protect the host residing in an area where there is little sunlight during the winter months. There are many interesting avenues to be explored before those environmental factors which are favorable to the rheumatic subject can be utilized in geographic locations where rheumatic fever is prone to occur.

B. *The Prevention of Implantation of Hemolytic Streptococci in the Nasopharynx.*—At this date, the only available method of preventing the implantation of hemolytic streptococci in the nasopharynx is the use of a chemoprophylactic agent which competes effectively with an essential growth factor for a position in the bacterial cell and prevents multiplication of the microorganisms.

Competitive inhibition is a well recognized phenomenon in medicine and biochemistry. Practical application of the principle of competitive inhibition occurs daily in the use of sulfonamide drugs. Adequate concentrations of these chemotherapeutic agents interfere with the synthesis of substances essential to multiplication of the streptococcic cell. It is not yet known whether sulfonamide compounds interfere with the synthesis of a paraaminobenzoic acid complex or with the functioning of paraaminobenzoic acid in its catalytic state. Bacteria probably have many mechanisms for coupling paraaminobenzoic acid and acquiring its catalytic complex. Perhaps only one of these mechanisms is subject to competitive inhibition by sulfonamide compounds. Whatever the mechanism may be, competitive inhibition by sulfonamide compounds can occur if hemolytic streptococci are required to synthesize paraaminobenzoic acid. In contrast, yeast cells readily produce paraaminobenzoic acid, which permits them to multiply in the presence of sulfonamide compounds, and many bacterial cells probably have alternate pathways of intermediary metabolism which permit them to circumvent the competitive effect of sulfonamide molecules. One or both of these conditions probably exist in micro-organisms which show resistance to sulfonamide compounds. Although the phenomenon of bacterial resistance to sulfonamide compounds may appear to be an academic problem for the laboratory worker engaged in fundamental research, it is actually a highly practical clinical problem in the prevention of rheumatic fever.

Experience with mass chemoprophylaxis in the Navy has shown that the daily administration of 1 Gm. of sulfadiazine is highly effective in preventing the implantation of sulfonamide susceptible strains of hemolytic streptococci in the nasopharynx and consequently in preventing streptococcic infections of the respiratory tract and rheumatic fever. However, the limiting factor in this principle is the occurrence and spread of bacterial variants which are not susceptible to those chemotherapeutic agents whose action is reversed by paraaminobenzoic acid. Recent outbreaks of infections of the throat followed by rheumatic fever have been induced by hemolytic streptococci which show resistance in vitro to high concentrations of sulfonamide compounds but which show pronounced susceptibility in vitro to low concentrations of a number of other chemotherapeutic agents whose action is not reversed by paraaminobenzoic acid. These sulfonamide-resistant strains of streptococci were of types 17, 19 or 3. It has not yet been possible to detect an association between their origin and either chemoprophylaxis or chemotherapy.

There is great need at this time for studies directed toward determination of the exact conditions which permit the genesis and perpetuation of resistant strains of hemolytic streptococci. When these underlying conditions are defined there is good reason to believe that the dissemination of sulfonamide-resistant bacteria can be prevented or modified. Productive research can be expected if the following approaches are explored:

(*a*) Genetic studies to determine the factors involved in the development of sulfonamide-resistant variants.

(*b*) Comparative metabolism studies to determine differences in the biochemical behavior of parent (susceptible) and daughter (resistant) strains.

(*c*) A study of the form in which paraaminobenzoic acid exists in yeast cells.

(*d*) An investigation of the mode of synthesis of paraaminobenzoic acid conjugates in sulfonamide-resistant and sulfonamide-sensitive strains of bacteria.

(*e*) A search for the enzyme system in which paraaminobenzoic acid participates.

servations made in the United States Navy have also shown that type identification may be difficult at those times when and places where the pathogenicity of hemolytic streptococci was low. It appears that the loss of pathogenicity is accompanied with a loss in the type-specific antigens which permits serologic typing.

(*f*) A field study to determine whether the simultaneous administration of two chemoprophylactic agents with different modes of action will prevent the genesis of sulfonamide-resistant strains.

3. *The Inhibition of Communicable Strains of Hemolytic Streptococci.*—Rheumatic fever is a seasonal disease in most environments. This is due to the fact that the streptococcic epidemic process is seasonal. However, when a hemolytic streptococcus acquires sufficient communicability, it can give rise to outbreaks of respiratory disease and rheumatic fever during the summer months (see lecture I, table 2). Solution of the problem of preventing the dissemination of hemolytic streptococci depends, first, on recognition of the importance of the communicability of streptococci and, second, on defining this characteristic of the bacterium.

Hemolytic streptococci are among the most prevalent air-borne respiratory pathogens. When inhaled into the nasopharynx, the organisms usually succumb; they are, in general, not highly communicable. Certain strains, however, have great capacity for initiating and perpetuating an outbreak of respiratory disease. The genesis of such an outbreak of infections of the respiratory tract is determined by the capacity of the bacterium to reproduce rapidly in the presence of the inhibitory substances of the human nasopharynx. The acquisition of this capacity or property by the bacterial cell is conditioned by the interaction of the infected host and the micro-organism. If either the host or the respiratory pathogen establishes its supremacy with dispatch, it is unlikely that communicability will develop. If, however, the host is unable to terminate the disease process and the bacterium is unable to extend its invasion, a series of changes may occur in the bacterial cell. Under these conditions of continued mild, subacute disease, the micro-organism is forced to adapt itself to the changing immune state of the host in order to maintain its activity. In making these adaptations to factors within the host, the micro-organism gives rise to bacterial cells endowed with the capacity to multiply in the presence of the inhibitory substances of the normal mucous membranes. The acquisition of this capacity by these cells permits them to survive when transmitted to the nasopharynx of a new host. These cells have thereby acquired communicability; they are "host fast." Communicability is usually lost in the newly infected host. It seems to persist in certain convalescent carriers for a period of weeks and may reappear during a virus infection. The acquisition of this characteristic by the bacterium does not, however, appear to be permanent.

Experiences in the Navy during World War II confirm earlier observations that many strains of hemolytic streptococci fail to spread and that a few strains become highly communicable. In Navy Training Centers a large majority of the streptococcic infections are attributed to a relatively few highly communicable strains of these pathogens. These communicable strains initiate and perpetuate an epidemic process. The transfer of a few recruits who have been infected with highly communicable strains of hemolytic streptococci has given rise to epidemics in the camps where these men are seeded. In some instances these secondary epidemics have occurred in geographic locations and under conditions which are not favorable to the dissemination of air-borne pathogens of the respiratory tract. These observations indicate that certain strains of hemolytic streptococci may become almost as communicable as the virus of measles.

Although the genesis of communicability may depend on concomitant virus infections, there is good reason to believe that the capacity of the micro-organism to infect readily may become an acquired characteristic of the bacterium which persists for some weeks. As a working hypothesis, it is suggested that "communicability" is associated either (*a*) with the development of some intracellular enzyme which makes possible rapid bacterial multiplication in the human nasopharynx or (*b*) with the inhibition of an intracellular enzyme system which ordinarily suppresses the bacterial component essential for implantation.

Most persons who carry hemolytic streptococci in their throat flora do not give rise to cross infections. However, a few convalescent patients disseminate communicable strains of hemolytic streptococci and spread contagion. These persons usually manifest evidence of mild persistent disease, such as sinusitis. They are "dangerous carriers." If the genesis of the streptococcic epidemic process is to be attacked, one must prevent the complications of nasopharyngitis. An important clinical problem awaiting solution is the suppression of discharges from the nose and throat of convalescent carriers of hemolytic streptococci. This attack requires a therapeutic weapon for eradicating the dangerous carrier state by preventing continued streptococcic activity in convalescent patients. To accomplish this there is need for intensive research on "anti-vitamins" which will compete successfully with other growth factors essential for survival of the streptococcic cell.

There are also interesting avenues to be explored in the bacteriology laboratory. For example, one might begin a study of determining

(*a*) whether highly communicable strains are rich in hyaluronic acid and deficient in hyaluronidase, (*b*) whether they contain antilysozyme and (*c*) whether they are peculiarly rich in M substance. Comparative studies of the cell constituents and the metabolism of different strains may be expected to produce leads. Promising leads can then be tested out in human volunteers. Identification of "the communicability factor" can reasonably be expected to suggest means for preventing its perpetuation and perhaps also its development. It is obvious that this is a key problem in the epidemiology of bacterial infections of the respiratory tract and that its solution must stem from long term fundamental research. One can visualize the possibility that the "X system" of the bacterium, which permits communicability, may be extremely sensitive and that the spread of contagion may be modified by some simple procedure.

In conclusion, any discoveries which can be applied to the problem of preventing streptococcic infections of the upper respiratory tract can be expected to lower the incidence of rheumatic fever.

II. THE APPLICATION OF ACTIVE IMMUNIZATION AGAINST RHEUMATIC FEVER

There are at least two possibilities for active immunization: (*a*) against streptococcic nasopharyngitis and (*b*) against the rheumatic reaction to streptococcic infections.

(*a*) *Against Streptococcic Infections.*—There is good clinical evidence that man fails to develop an adequate immunity to group A hemolytic streptococci. It is not known whether a streptococcic infection induces type-specific immunity. At one naval activity recruits were immunized actively with type 17 and type 19 vaccines. These vaccines were prepared from the prevalent epidemic strains by killing the bacteria with either heat or ultraviolet rays. This attempt failed to lower the incidence of streptococcic infections caused by types 17 and 19. At the present time it seems unlikely that one can use active immunization to protect against streptococcic nasopharyngitis, which may be caused by innumerable antigenically different strains of hemolytic streptococci. Nevertheless, it will be of interest to determine whether inoculations with the M substance (fortified by an appropriate adjuvant) of an epidemic strain of hemolytic streptococci will confer temporary type-specific immunity in man.

(*b*) *Against a Rheumatic Reaction Following Streptococcic Infection.*—It seems possible that the reactivity of a rheumatic subject to hemolytic streptococci can be modified. Interesting immunizing agents will become available when the "rheumatogenic factor" in group A hemolytic streptococci is determined and when the sensitizing complex, which I believe to be formed in phase 2, is identified. At present one may begin empirically by making a conjugate of streptococcic products with material from human endothelium or by preparing a histamine azoprotein. It will be of great interest to determine whether active immunization with either of these complexes modifies the reactivity of the rheumatic subject to infections by hemolytic streptococci.

III. THE "RHEUMATOGENIC" FACTOR IN HEMOLYTIC STREPTOCOCCI

It has already been pointed out that some strains of hemolytic streptococci precipitate rheumatic attacks and that other strains of the same serologic type fail to induce rheumatism in rheumatic subjects. The "rheumatogenic factor" of hemolytic streptococci appears to be a strain characteristic. However, nothing is known of its nature.

Comparative analyses of the metabolism, constituents and products of "rheumatogenic" and of nonrheumatogenic strains of hemolytic streptococci may help to identify the streptococcic factor associated with the genesis of the rheumatic attack. The identification of the "rheumatogenic factor" in streptococci will make possible the studies in active immunization outlined previously.

IV. A DEFICIENCY IN ANTIBODY PRODUCTION BY THE RHEUMATIC SUBJECT

My associates and I have reported a number of studies indicating that the immune response of a child in whom a rheumatic attack develops differs from that of a nonrheumatic subject who makes an uncomplicated recovery from streptococcic nasopharyngitis. During the course of these studies, Dr. Edgar Todd and I observed that the patient with rheumatic fever appeared to be deficient in one streptococcus antibody. In contrast to the high level of antistreptolysin O antibody which accompanies rheumatic fever the level of antistreptolysin S tends to be low. We found that the titer of antistreptolysin S rose considerably above the normal level of the serums of nonrheumatic children and in the serums of rheumatic children who escaped rheumatic recrudescences following streptococcic infections. However, in rheumatic children in whom recrudescences developed after streptococcic nasopharyngitis, the antistreptolysin S titer appeared to remain low. The titer of this antibody continued to be low in the serums of

these patients during the period of rheumatic activity. Furthermore, the titer varied with the intensity of rheumatic activity, tending to be lowest when the clinical manifestations were severest. These observations indicated that there may be an interesting relation betwen rheumatic activity and the antibody response to this extremely toxic antigen. Further investigations of the possible inadequacy of the rheumatic subject to handle streptolysin S in the usual manner are to be desired.

Two additional studies may be directed to test the hypothesis that there is a defect in the production of antibody by the rheumatic subject:

(*a*) By electrophoretic separation, the gamma globulin of rheumatic patients can be isolated. The amino acid content of streptococcus antibody developed during phase 2 of a rheumatic attack can be determined and compared with that of nonrheumatic subjects who have made an uneventful recovery following scarlet fever.

(*b*) One can also determine whether the rheumatic subject's development of antibody to typhoid vaccine or other bacterial antigens is similar to that of the nonrheumatic subject or whether the development is delayed or of lesser degree.

There is need for careful biologic and biochemical studies on the immune responses of the rheumatic subject. If a defect can be detected, corrective measures may be applied, perhaps either by the reenforcement of diet or by active immunization.

V. REACTIVE SUBSTANCES INDUCED IN MAN BY INFECTION

One of the most interesting fields for medical research is in the group of diseases which appear to be postinfectious processes. Closely associated with these obscure diseases are peculiar alterations in host metabolism. These alterations are reflected by the presence of abnormal proteins in the serum. Some of these abnormal proteins are reactive substances. In disseminated lupus erythematosus, we have observed a gamma globulin which reacts in vitro with the phospholipids used in the serologic tests for syphilis. In many febrile infectious processes, a substance is present in the serum albumin which reacts with the C polysaccharide of pneumococci. Avery and his co-workers have shown that this interesting reactive substance can be differentiated from normal constituents of human serum, that it has immunologic specificity and that it is highly antigenic.

Reactive substances appear in the serums of patients during a rheumatic attack. One of these reacts with the C polysaccharide of pneumoccocci. Another precipitates a substance present in the serum during a part of phase 2, a few days before the onset of rheumatic activity. This reactive substance does not appear to be a streptococcus antibody; it is not absorbed with killed organisms of the strains of hemolytic streptococci with which the patient was infected.

Studies by Dr. Herbert Wilcox and I failed to show that this reactive phase 3 substance is antigenic. We attempted to sensitize guinea pigs with this substance. First, the guinea pigs were desensitized to human serum. Phase 3 serum was then injected into these animals. At the appropriate time for producing anaphylaxis, phase 3 serum was perfused through the isolated guinea pig's heart attached to a kymograph which recorded the coronary flow. Using this technic, we were unable to induce manifestations of anaphylaxis with rheumatic fever serums containing the reactive substance.

Future studies should be designed (*a*) to concentrate and purify this phase 3–reactive substance, (*b*) to learn whether it can be absorbed with human tissues, (*c*) to determine whether it is antigenic and (*d*) to define its character. The acquisition of information on the nature of this substance may be expected to throw light on the mechanism of rheumatic fever.

We have also considered the possibility that this phase 3 substance or some other constituent of the patient with rheumatic fever has the capacity to react with and cause injury to the capillaries. To test this hypothesis, Dr. Howard Bruenn and I made some preliminary studies. Although we were unable to draw conclusions from the results obtained, I believe that further studies with concentrated material may prove interesting, and for this reason I shall summarize our observations briefly.

Human serum in doses of 5 to 8 cc. was injected intravenously into 45 collie puppies weighing between 5 and 10 Kg. Some of the animals received a single dose; others received repeated doses at intervals of one or two days over a period of one month. Electrocardiograms were made before each injection and during the interims. The animals were killed at varying intervals.

The electrocardiographic data and the anatomic changes observed were briefly as follows:

(*a*) Twelve rheumatic fever serums induced striking electrocardiographic changes, and in 8 of 12 animals there were gross cardial lesions.

(*b*) Twelve rheumatic fever serums failed to induce any changes.

(*c*) Eight rheumatic fever serums induced equivocal electrocardiographic changes, but no anatomic lesions were detected.

(*d*) Thirteen normal or pathologic serums (other than rheumatic fever) failed to induce electrocardiographic or anatomic changes in the heart.

The electrocardiographic abnormalities were: inversion of the T wave in lead I in each animal, notching of T waves in leads II and III in several instances and right preponderance in 2 instances. In some animals these changes were evanescent; in others they persisted for several days and in 1 they were present for a month.

The anatomic changes observed in 8 animals were most striking in the heart. The lesion in each instance was hemorrhage. Subendothelial hemorrhages occurred in the chambers of the left auricle and the left ventricle. In some animals all these hemorrhages were extensive; in others there were petechial hemorrhages and extravasations of blood as shown in the colored drawing. None of the specimens showed microscopic evidence of injury to blood vessels, of alteration of collagen or of formation of Aschoff's bodies.

It appeared that the electrocardiographic changes and hemorrhagic lesions were induced by phase 3 rheumatic fever serum. Whether this was due to anaphylaxis or to injury caused by a reactive substance in the serum was not determined. Further studies on the substances which appear in rheumatic fever and which do not occur as constituents of normal serum are to be desired.

VI. THE NEED OF A TEST FOR IDENTIFYING RHEUMATIC ACTIVITY

Our laboratory has made a number of unsuccessful attempts to extract from the urine and serum of patients with rheumatic fever substances which induce specific cutaneous reactions during rheumatic activity. By appropriate precipitation procedures, with alcohol and acetone, one can recover "urine colloids" which are of some interest. Urinary excretion products not present in phases 1 or 2 but appearing in phase 3 cause an immediate wheal and erythema cutaneous reaction and an intense erythematous nodular reaction in twenty-four hours when injected intracutaneously into the skin of a rabbit. Furthermore, these "colloids" sensitize the animal in about ten days. Separation of these excretory products and their purification may lead to the detection of a substance suitable for the cutaneous testing of man and useful in detecting rheumatic activity.

A complement fixation test may prove to be a more attractive means for identifying rheumatic activity. Miss Ruth Pauli and I obtained some evidence that the livers of patients dying during fulminating rheumatism may contain an antigen suitable for this purpose. In our hands, this approach has been complicated by the facts that reactive substances extracted from the livers of patients with fulminating rheumatic fever have been stable for only six months, and it has been difficult to prevent anticomplementary reactions.

Our preliminary observations with a complement fixation test may be summarized as follows:

1. There appeared to be an interesting antigenic substance in the livers of patients dying with intense rheumatic fever.

2. This antigen, when appropriately diluted for the complement fixation test, was found to be fixed by the serum of patients with rheumatic fever and not by the serums of normal persons or patients with other diseases, with one exception.

3. This exception proved to be persons of blood group AB. Serums from these persons reacted more strongly than serums from patients with rheumatic fever with the antigen that was obtained from liver material.

4. The intensity of the complement fixation reaction in rheumatic fever paralleled the intensity of the disease, seemed to be cyclic, was not modified by salicylate therapy and was independent of the blood sedimentation rate.

5. Extracts and fractions of liver extracts obtained from a few patients dying of infectious diseases did not contain the antigenic substance which was reactive with rheumatic fever serums.

The present problem is to make suitable extracts of liver material obtained from patients dying of fulminating rheumatic fever, to remove fat and the antigens which react with blood group AB and to obtain a stable antigen which can be used in a complement fixation test without causing an anticomplementary reaction. The development of a specific test will make possible accurate diagnosis and eliminate a variable which gives rise to inconsistencies in research on rheumatic fever.

VII. THE PROBLEM OF MODIFYING SUSCEPTIBILITY TO RHEUMATIC FEVER BY ALTERING THE ENDOCRINE BALANCE

It is generally recognized that puberty and pregnancy decrease susceptibility to rheumatism. Little is known about the balance of androgens and estrogens in rheumatic subjects. The possibility that androgens and estrogens if administered during a rheumatic attack may modify the course of the disease has, to my knowledge, not

Heart of Collie puppy killed twenty-four hours after receiving an intravenous dose of 5 cc. of serum from a patient with intense rheumatic fever. The hemorrhages are subendothelial.

et been tested. Since, however, it is known hat testosterone will increase the storage of rotein and calcium and since the diets of most heumatic children appear to be deficient in these ctors, it will be interesting to make metabolic tudies on rheumatic patients with polycyclic tacks, before and after the administration of stosterone. The possible dangers of such a study re obvious.

It has long been recognized that there is some ommon factor between the person in whom xophthalmic goiter develops and the rheumatic ubject. Rheumatic fever occurs more frequently n the hyperthyroid subject than among the verage population. The two diseases have a imilar geographic distribution, and both may be recipitated by hemolytic streptococcus naso-haryngitis. The association between the two iseases is probably more intimate than is gen-rally appreciated.

Our studies of approximately 500 rheumatic milies over a period of fifteen years have con-rmed the reports of previous observers. In sev-ral instances, the two diseases occurred con-urrently in the same patient. A number of the heumatic children in our group had a familial istory (maternal) of exophthalmic goiter. Hyperthyroidism later developed in some of the heumatic children under our care, and some of he rheumatic adults later became hyperthyroid. urthermore, in several adult patients who came nder our observation, intense rheumatic pan-arditis developed while they were receiving thy-oid. These persons had previously experienced treptococcic diseases but had escaped rheumatic anifestations until they contracted a strepto-occic infection while receiving therapeutic doses f thyroid.

The collected observations indicate that there probably a constitutional defect common to hese two disease processes and that perhaps yperthyroidism increases rheumatic suscepti-ility.

It seems to us that this defect may well be etabolic. It has been reported that thyrotoxic atients have a number of vitamin deficiencies nd that the blood levels of thiamine and diphos-hothiamine are low in this disease. There can e no doubt that the relation between the func-ons of the thyroid gland and cellular oxidation s an intimate one. But information is lacking on he metabolism of the hyperthyroid subject with-ut thyrotoxicosis. One now needs to know what bnormalities in metabolism predispose to the evelopment of exophthalmic goiter, for these ame abnormalities may well play a role in the enesis of the rheumatic state. These investiga-tions will require years of fundamental work on enzymic reactions. Meanwhile, one can make a clinical study to determine whether the administration of thiouracil in phase 2 or the first cycle of phase 3 will modify the rheumatic process. We have observed that total ablation of the thyroid gland appeared to lower the susceptibility of rheumatic subjects to recurrences. If thiouracil lowers susceptibility to rheumatism, it will be of great interest to make exhaustive metabolic studies on these patients before and after the administration of thiouracil.

VIII. THE SIGNIFICANCE OF NUTRITION IN THE RHEUMATIC STATE

That rheumatic fever is essentially a disease of the underprivileged seems to be established. However, the factors of poverty that are concerned with conditioning the rheumatic host are obscure. Overcrowding predisposes to hemolytic streptococcus pharyngitis; yet the healthy child, although he may contract many streptococcic infections, nearly always escapes rheumatic fever. One factor of poverty that has attracted interest in recent studies on rheumatic fever is nutrition. Clinical observations have indicated that the state of metabolism of the host may exert an effect on susceptibility to rheumatic fever. The host with a high blood lipid level, whether this be due to nephrosis, diabetes or total thyroidectomy, seems to be refractory to rheumatic fever. In contrast, the patient with exophthalmic goiter and the patient receiving therapeutic doses of thyroid may manifest unusual susceptibility to rheumatic fever. Although it is not yet possible to interpret the influence of metabolic states on the host's reactions to infection, future developments in biochemical research can be expected to show a close relationship.

Just prior to the outbreak of World War II and the institution of the rationing of food, Dr. Lucile Moore and I began to test the possible effectiveness of reenforcing the diets of subjects with quiescent rheumatic fever. The study was designed to determine whether rheumatic susceptibility could be modified by this means. Three groups of underprivileged children attending school in New York city were selected. The size of each group was limited to about 30 subjects; each subject was selected because noticeable susceptibility to rheumatic fever had been observed.

One group received a daily diet which included the following constituents: 1 quart (0.95 liter) of milk, two eggs, one serving of meat, two servings of fruit, two green vegetables, three pats of butter and halibut liver oil with viosterol

(8,500 U. S. P. units of vitamin A and 1,700 U. S. P. units of vitamin D). A second group received its customary diet reenforced only with large amounts of powdered egg yolk. The third group, which served as a control, continued to receive the diet of underprivileged children in New York city. This diet is known to be deficient in protein, vitamin A, calcium and iron.

During this one year's observation, in 38 per cent of the control group rheumatic fever developed. The incidence of rheumatic attacks in the group on the selected diet was 6.7 per cent, and the incidence among the group receiving the normal diet reenforced with egg yolk was 5 per cent. An ancillary study showed that reenforcement of the normal diet with a daily dose of 3 Gm. of paraaminobenzoic acid did not prevent streptococcic infections or rheumatic fever.

It is our opinion that some dietary factor or factors, as yet undetermined, may modify rheumatic susceptibility and that clinical investigations directed to identify these factors may make valuable contributions to preventive medicine.

IX. THE APPLICATION OF A REENFORCED DIET DURING PHASE 2

We have also been interested in determining whether the evolution of the rheumatic attack can be modified in phase 2 by dietary measures. One preliminary study was made in 1942 and 1943. Twenty highly susceptible rheumatic children were given large doses of powdered egg yolk (daily dose equivalent to four egg yolks) for three weeks following streptococcic infections of the throat. These infections gave rise to an incidence of rheumatic fever of about 35 per cent in controls. All the children on the reenforced diet escaped rheumatic fever, with 1 exception. This child, who had a mild attack, ingested the egg yolk irregularly and omitted it entirely for four days during phase 2. Carefully controlled studies on the possible influence of diet during the period of recovery from streptococcic infections can be made in scarlet fever wards and in institutions caring for rheumatic children. In our opinion, this is an attractive field for clinical research. The investigator must bear in mind, however, that the administration of sulfonamide compounds in therapeutic doses during phases 1 and 2 may enhance rheumatic susceptibility and neutralize the possibility of benefit from dietary factors.

X. THE PROBLEM OF THE ROLE OF LIPIDS IN RHEUMATIC FEVER

One of the most interesting biologic problems to be investigated in rheumatic fever is the role of fats in this postinfectious disease process. In vitro, the presence of fat interferes with the formation of streptolysin. It may well be that a high concentration of lipids interferes with antigen formation in vivo. Although children with nephrosis are prone to contract streptococcic infections of the respiratory tract we have been unable to find a single report of pathologic examination in a case in which rheumatic lesions were noted at autopsy. We have observed the development of lipemia in 1 rheumatic child, who had seemed to be a most susceptible subject, and his death a few years later at the age of 18 following repeated streptococcic infections. At autopsy, he had advanced arteriosclerosis and stigmas of aortic and mitral valvular disease; however, no fresh rheumatic lesions were detected.

These clinical observations led Dr. Kennet Turner and me to make some preliminary studies on cholesterol metabolism in the rheumatic patient. Our subjects were ambulatory, rheumatic children in New York, rheumatic children at the Pelham Home and nonrheumatic student nurses. We were particularly interested in blood levels of total cholesterol. The observations in these preliminary studies suggested that there is a relation between rheumatic activity and cholesterol metabolism. Further investigations are to be desired. Our observations were in brief:

1. Rheumatic subjects in good health had the same blood levels of cholesterol as nonrheumatic subjects.

2. Rheumatic subjects with streptococcic infections of the throat, like nonrheumatic subjects, showed either no change or a slight fall in the blood level of cholesterol.

3. The onset of a rheumatic attack was accompanied with a significant fall in the blood level. This blood level remained normal if the rheumatic subject escaped an attack following streptococcic pharyngitis.

4. There appeared to be a parallelism between the degree of fall in the blood level and the intensity of the rheumatic attack.

5. In several cases which terminated fatally there were the lowest blood levels of cholesterol recorded in this series.

6. Recovery was followed by or accompanied with a return of the blood level to normal. But with a recurrence of symptoms in a polycyclic attack the blood level again fell.

Attempts to modify rheumatic activity by high fat diets have to date been unsuccessful

Attention is, nevertheless, called to the possibility that the intravenous administration of lipids, or some other harmless fat, in phases 2 or 3 may modify the rheumatic process. It will be of interest to determine whether the intensity of rheumatic activity can be lessened by this procedure.

XI. THE PROTECTION OF THE CONNECTIVE TISSUES OF THE RHEUMATIC SUBJECT DURING PHASE 3

Attempts to modify the course of a rheumatic attack by diet have been uniformly unsuccessful. Nevertheless, there is good reason to believe that during phase 3 the degree of injury to the tissue may be lowered by an abundance of some dietary factor. The great advances made in the application of reenforced diets to protect the liver against poisoning by many agents gives an indication of what may be accomplished. The demonstration that chronic hepatic cirrhosis can be reversed by dietary measures serves as an example.

Two studies on the use of diet for the protection of connective tissue suggest themselves. One might use experimental animals in which vascular lesions can be produced by sulfonamide compounds, by desoxycorticosterone or by other means and determine whether any dietary factors will prevent or minimize the development of these vascular lesions. A second, and more direct, approach may be made by testing the effect of high concentrations of proteins, casein hydrolysate or an essential amino acid, such as methionine, during the first cycle of phase 3. The time is now appropriate for determining whether amigen or essential amino acids will afford protection for the tissue against the injurious effects of the rheumatic process or will aid in the reparative processes which follow a rheumatic attack.

XII. THE PREVENTION OF POLYCYCLIC RHEUMATIC FEVER

If the rheumatic attacks were always monocyclic, the problem of rheumatic fever would be comparable to the problem of acute hemorrhagic nephritis. In children, however, rheumatic disease is usually polycyclic. This makes the problem comparable to that of subacute or even chronic nephritis. During each cycle of the rheumatic process, severe inflammatory processes occur in vascular tissues. One of the most important problems now confronting the clinician is the prevention of the polycyclic rheumatic attack. There are several promising approaches to this challenge.

One possibility is the suppression of antigen formation by concentrated gamma globulin or by the administration of normal human plasma or, as indicated in a preceding section, by lipid therapy or by reenforced diets.

A second possibility is passive immunization with streptococcus antibodies. Whatever is the reason for continued activity of hemolytic streptococcus in the rheumatic subject, it seems to us that its antigenicity may be suppressed by supplying the proper antibody to the patient at the end of the first cycle of an attack. We have made some preliminary observations on this point. Convalescent scarlet fever serum was administered to 20 patients in New York city. They were all children or young adults with active carditis and polycyclic rheumatic attacks. Two patients received serum during a febrile period of the cycle and reacted unfavorably. Eighteen patients were treated during the afebrile phase of a rheumatic cycle. Fourteen of these recovered without the development of another cycle and 4 had milder activity thereafter. The batches of pooled serum which appeared to give benefit were obtained during the late winter or early spring months at Willard Parker Hospital. The ineffective batches of serums were obtained during the fall months.

It seems to us important that type-specific antistreptococcus serums be prepared. These materials can be given without danger at the end of the first rheumatic cycle. If passive immunization, either with rabbit globulin containing antibodies to Lancefield's M substance or with type-specific human serum, will modify the natural course of a rheumatic attack in childhood, the therapeutic problem of rheumatic fever will be simplified.

One nonspecific measure for modifying polycyclic rheumatism which may readily be tested in the armed forces is the influence of sunshine on recovery from rheumatic fever. Certain military personnel with rheumatic activity are of necessity treated indoors during the winter and spring months. Others are treated in environments where sunshine abounds and where patients' beds can be placed outdoors almost daily. Carefully controlled clinical studies of comparable groups treated under different environmental conditions may supply an answer to the question of the possible value of sunshine in terminating rheumatic activity.

The use of salicylates at the onset of a rheumatic attack in dosage adequate to reduce to a minimum damage to tissue from the rheumatic process was discussed in the first lecture. Al-

though useful and fascinating to study, the salicylates do not appear to be the final solution to this problem. Other measures must be developed to terminate rheumatic activity. The development of these measures will come from studies on the enzyme activities of hemolytic streptococci and the abnormal metabolic reactions induced in the host. These studies will require close collaboration between the laboratory and the clinic. The acquisition of tools to prevent polycyclic rheumatic activity will permit the physician to check the progress of carditis, which frequently leads to incapacitating heart disease.

A PERSPECTIVE OF RHEUMATIC FEVER

Scarlet fever was long considered a specific infection. Now it is known that scarlet fever is a manifestation of any group A streptococcic disease in which the bacterial agent produces sufficient erythrogenic toxin in a susceptible host. Likewise, rheumatic fever has long been considered to be a specific infection. Before concluding these lectures, I should like to invite attention to the concept that the term "rheumatic infection" is a misnomer and that rheumatic fever may be a biochemical reaction of man.

The child who dies during the first week of the first attack of rheumatic fever has no Aschoff bodies in the myocardium. The heart is dilated, and endocardial changes are manifest. Microscopic examination of the endocardium reveals verrucae composed of ruptured endothelium, edema and a mass of granular eosinophilic material. No organisms are seen, and the lesion is sterile on culture. The origin of the lesion appears to be in the subendothelial or the endothelial cells. Although the microscope affords a picture of the morphologic changes that have occurred, it gives no indication of the biochemical lesion and the disturbances in cellular physiology that have preceded this exudation. Until the biochemist analyzes and identifies the changes concerned in the pathogenesis of this exudative lesion, investigators must be satisfied with a working hypothesis which will permit them to attack the problem of the rheumatic mechanism.

Most of the degenerative diseases of early or middle life appear insidiously and cause a high mortality. Of those chronic illnesses which follow injury to the small blood vessels, the initiating factors and the pathogenesis are unrecognized. However, in rheumatic fever, the investigator can recover the initiating agents, hemolytic streptococci, at the onset of infection; he can observe the patient make an apparently satisfactory clinical recovery, and he can then detect the development of a rheumatic attack two weeks later. Careful clinical observations on the sequential development of rheumatic fever suggest that the evolution of the rheumatic attack may well be as follows: Heredity produces about 5 per cent of persons with a mendelian recessive characteristic which is called rheumatic susceptibility. The diet of the underprivileged is conducive to mild deficiencies in metabolism and increases susceptibility of the host. The conditioned, susceptible host is unable to terminate an acute mild streptococcic infection promptly. Instead of effecting a temporary immunity, the rheumatic subject becomes sensitized to some antigenic complex in which there is a streptococcic component. The continued elaboration of this complex gives rise to abnormal biochemical reactions of the sensitized cells of the reticuloendothelial system.

One can reasonably assume that abnormal reactions of sensitized cells modify the balance of intracellular enzyme systems and cause biochemical lesions. With the occurrence of a biochemical lesion, abnormal metabolites are formed. Some of these substances may be injurious to vicinal tissues. For example, if histidine, which is ordinarily decarboxylated, is deaminized, histamine is formed. The liberation of histamine-like substances may alter vascular permeability. The working hypothesis offered in this lecture is that infection leads to an abnormal immune state in which occur biochemical lesions that induce rheumatic phenomena.

CONCLUSION

I have tried to outline a concept of rheumatic fever and to define some of the unknowns. There are many interesting rheumatic problems awaiting solution by the students of bacteriology, immunology, metabolism and biochemistry. These problems cannot be solved in a lower animal; they can be solved only in man. It is therefore necessary that attacks on these problems, if they are to be effective, be made both in the clinic and in the laboratory. The clinician must work with healthy rheumatic subjects whose life histories are carefully observed and recorded, patients with acute rheumatic disease and convalescent rheumatic patients. The laboratory group must include a team of workers who, as biologists and biochemists, can collaborate fully with the clinician in bringing pertinent problems into sharp focus and in selecting those problems which can be solved with technics now available.

Because these lectures were written under unusual conditions during military assignments it has not been possible to include references to the many investigators whose observations have helped in the preparation of the lectures.

Obituaries

CHARLES GILMORE KERLEY, M.D.

1863-1945

Dr. Charles Gilmore Kerley died in New York Sept. 7, 1945, two years after his retirement. His fifty-five years of practice was wholly unique because of the individuality and volume of work performed.

After his graduation from New York University Medical College he studied in Munich and Vienna and then returned to the United States as an associate of the late Dr. L. Emmett Holt.

Dr. Kerley's practice grew phenomenally not only because of its timely beginning when pediatrics was a new specialty but also because of his insight, resourcefulness and unceasing application. He succeeded Dr. Holt as professor of pediatrics in New York Polyclinic Medical School and Hospital, holding the position for fifteen years and serving as a consultant until his death. He was attending physician and later consultant at the Babies Hospital and attending physician at the New York Nursery and Child's Hospital. Eventually he became a consultant at twelve institutions, including the Sharon Hospital, at Sharon, Conn., where plans have been drawn to erect a children's wing, to be known as the Charles Gilmore Kerley pavilion.

Dr. Kerley is credited with the writing of more than three hundred papers and six books. His outstanding work was a book designed for the general practitioner, published in 1907 and superseded by "Practice of Pediatrics" in 1914. A final edition, largely rewritten, was completed in 1924.

Dr. Kerley had been president of the American Pediatric Society and the New York County Medical Society and was a founder member of The American Academy of Pediatrics.

Few self-reliant men of great versatility have pursued ideals so devotedly.

G. W. G.

News and Comment

GENERAL NEWS

A Program for the Care and Rehabilitation of Asthmatic Children.—It is estimated by leading allergists that 14,000,000 Americans are affected by some form of allergy and that allergy definitely handicaps 1,400,000 annually. What is even more striking, 1 in every 10 is affected seriously. Allergy is a chronic condition. It begins in infancy and remains throughout a lifetime.

About five years ago, conscious of the need for the treatment and rehabilitation of underprivileged children suffering from acute bronchial asthma and other refractory diseases of the upper respiratory tract, the National Home for Jewish Children at Denver undertook the care of such patients, for nowhere else in the country is there a place for children with such intractable conditions when a physician recommends a change in climate and environment.

In the mile-high, dry climate of Denver, in an area comparatively free from dust, this Home is located, nestled in the foothills of the Rockies. To it come these children, selected with the utmost care on the basis of physicians' recommendations and intensive and thorough social studies of the home environment made by trained case workers. They come from all parts of the country, remaining until physicians again say that they are sufficiently on the road to good health that they may return to their own homes.

In a comparatively normal environment and sharing the companionship of other children, the asthmatic child is under expert medical supervision at the Home and is cared for by a staff trained in child welfare. During his stay, periodic examinations are made and full reports given to the referring physicians and hospital clinics. The National Home has a modern, well equipped infirmary where children requiring bed care are attended by registered nurses under the supervision of the attending physicians. The children are housed in attractively furnished congregate cottages. Each child is afforded the privacy of an individual bedroom. Food of the highest quality is carefully prepared in modern kitchens, and special diets are given when prescribed by physicians. The children participate in the community life by attending the local schools and taking part in communal recreations.

In addition to the intensive preparation made prior to the children's admission to the Home, an equally thorough program of after-care is carried out on the return of the child to his family. The aim of this program is to make certain that the child will continue to enjoy his restored health in the very environment which originally was a factor contributing to his illness. Trained social workers educate the parents in the general health practices which play an important part in the treatment of allergic diseases.

Dr. M. Murray Peshkin, chief of the Children's Allergy Clinic of Mount Sinai Hospital of New York City, and chief consultant physician of the National Home states: "The National Home for Jewish Children at Denver, through a fortuitous combination of climate and environment, has brought remarkable relief to many children suffering from chronic bronchial asthma and other allergic respiratory diseases. The Home has amply demonstrated that complete recovery from asthma can occur in these cases heretofore regarded as hopeless. It has the most ideal setup I ever saw; the only place of its kind in America for the care of asthmatic children."

Dr. Leon Unger, of Chicago, assistant professor in the department of medicine, Northwestern University Medical School, in his recently published textbook "Bronchial Asthma," stated: "In the past few years a number of asthmatic children have been greatly improved by removal to the National Home for Jewish Children located at Denver, Colorado. Much of this success is undoubtedly due to improvement in climate. Much is also due to change in environment, with removal from dusty homes, and in some cases, from overzealous parents."

The Home opens its doors to children whose families cannot afford the extensive and costly private care necessary to alleviate the suffering of their youngsters. Application may be made by communicating with the Social Service Department of the National Home for Jewish Children, 1457 Broadway, New York 18, or through the office of the Jewish Social Service Organization in any community.

Reprints for the Devastated Medical Libraries of Manila.—In connection with its campaign to help rebuild the medical libraries of Manila which were destroyed during the Japanese occupation, the Academy of International of Medicine requests that medical authors contribute eight or ten reprints of each of their articles which have been published since 1941. They may be sent at the regular parcel post rate of 16 cents for the first pound and 11 cents for each additional pound, care of A. B. M. Sison, M.D., Philippine General Hospital, Manila, P. I.

Back Numbers Wanted.—A correspondent in one of the Dutch universities is anxious to secure the complete issues of volume 61 (1941) and volume 65 (1943) of the AMERICAN JOURNAL OF DISEASES OF CHILDREN.

If any of the readers have one or more of these issues that they can spare, I shall appreciate it if they will send them to me, so that I in turn may forward them to our correspondent.

C. G. GRULEE, M.D., Editor.

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

COMPARISON OF PATHOGENICITY TESTS FOR STAPHYLOCOCCI. R. SALM, Edinburgh M. J. **52**:22 (Jan.) 1945.

This study was made in the department of bacteriology, Edinburgh Royal Infirmary. Unselected strains of staphylococci were tested for pathogenicity. Of the three hundred and twenty-five different strains, two hundred were strains of Staphylococcus aureus and one hundred and twenty-five of Staphylococcus albus. It was found that if a strain will ferment three or four of the carbohydrates used there is a greater probability that it will prove to be pathogenic.

NEFF, Kansas City, Mo.

Metabolism; Infant Feeding; Milk and Other Foods

NUTRITIONAL ASPECTS OF GLOBULIN METABOLISM. PAUL R. CANNON, J. Allergy **16**:78 (March) 1945.

This article consists of a short discussion of the chemical makeup of plasma globulin and antibody globulin. Evidence indicates that gamma globulin contains many of the amino acids necessary to keep the body in nitrogen balance. Evidence is accumulating that shows that antibodies are modified serum globulin and that most antibodies occur in the gamma fraction of immune serum globulin. The feeding of amino acid to protein-depleted animals will increase plasma protein, including both plasma albumin and globulin; the antibody globulin also participates in the increase. "The implication is that the fabrication of antibody globulin is a part of the general process of protein metabolism and that, for this reason, acquired resistance depends, in last analysis, upon the processes of nutrition."

HOYER, Cincinnati.

ABSORPTION OF FERROUS AND FERRIC RADIOACTIVE IRON BY HUMAN SUBJECTS AND BY DOGS. CARL V. MOORE, REUBENIA DUBACH, VIRGINIA MINNICH and HAROLD K. ROBERTS, J. Clin. Investigation **23**: 755 (Sept.) 1944.

Comparison was made in the same normal and iron-deficient human subjects and in the same normal and iron-deficient dogs of the degree to which comparable test doses of ferrous and ferric radioactive iron were assimilated. The quantity of iron given varied from 1 to 4 mg. of iron per kilogram of body weight. The amount of radioactive iron that subsequently appeared in hemoglobin in the peripheral blood was used as the measure of the amount absorbed. Under these conditions, human subjects absorbed one and one-half to fifteen times as much ferrous as ferric iron, while dogs either absorbed both valence forms to a comparable degree or showed preferential assimilation of ferrous salts.

GUEST, Cincinnati. [FROM THE AUTHORS' SUMMARY]

CITRATE METABOLISM OF PRESCHOOL CHILDREN. ESTHER RUTHERFORD METCALF and MILICENT L. HATHAWAY, J. Nutrition **29**:211 (March) 1945.

The citric acid metabolism of 4 preschool children was studied over an experimental period of sixteen weeks by Metcalf and Hathaway. The children were on a controlled diet which was supplemented with 100 mg. of ascorbic acid, 3.38 Gm. of potassium citrate or equivalent amounts of orange juice as indicated. On the basal diet, the 4 subjects excreted daily an average of 55, 93, 100 and 247 mg. of citric acid in the urine, or 3, 6, 7 and 13 mg. per kilogram of body weight. No relationship was found between "utilization" of ascorbic acid and citrate excretion. The addition of 3.38 Gm. of potassium citrate to the basal diet, with or without the addition of ascorbic acid, caused a definite increase in excretion of citrates consistent in amount for all 4 children, the average increase being 7.1 to 8.1 per cent of the added citrate intake. The addition of a quantity of orange juice containing an amount of citrate equivalent to that in the potassium citrate supplement caused an average increase in excretion of citrate of 2.8 to 7.0 per cent of the added citrate intake. In this study the increase in the intake of citrates was for each child about 80 mg. more when orange juice was given than when the potassium citrate was added, but the excretion was decreased by 44 to 95 mg. The urinary p_H was less alkaline with the orange juice than with the potassium citrate supplement, which confirmed the conclusion that the acid-base relationship is more important than the citrate content of the diet in controlling citrate excretion.

FREDEEN, Kansas City, Mo.

THE EFFECT OF SOY FLOUR ON THE NUTRITIVE VALUE OF THE PROTEIN OF WHITE BREAD. FRANCES E. VOLZ, R. M. FORBES, W. L. NELSON and J. K. LOOSLI, J. Nutrition **29**:269 (April) 1945.

Volz and associates reported on growth studies and biologic values which showed that the addition of 5 per cent of soy flour significantly improved the growth-promoting value of white bread which contained 3 per cent of whole milk solids. White bread containing 3 per cent milk solids gave a gain of 0.97 Gm. per gram of protein consumed, and bread with the addition of 5 per cent soy flour gave a gain of 1.17 Gm.; the biologic value of the protein was 43.3 for the white bread and 47.7 for the bread with 5 per cent soy flour (Mitchell method).

FREDEEN, Kansas City, Mo.

PRESENT KNOWLEDGE ON ADEQUATE NUTRITION IN INFANCY. F. W. SCHLUTZ, Rev. mex. de pediat. **13**: 101 (June-Aug.) 1944.

The author discusses present standards of nutrition for infants and children, following especially the figures given by the Food and Nutrition Board of the National Research Council of the United States. He describes the role of protein and essential amino acids, carbohydrates, fats, minerals and vitamins in the maintenance of the integrity of bodily functions. He gives the accepted figures regarded as minimal and optimal for different food elements at various ages. The studies of Boyd, of Iowa, on the effects of various diets on child health and development and the results of statistical studies compiled by Stiebering, of the United States Department of Agriculture, on the types of diets consumed by persons with different incomes are commented on in some detail.

The article does not lend itself to abstracting.

ABALLI, Habana, Cuba.

Vitamins; Avitaminoses

STUDIES IN DARK ADAPTATION AS A MEANS OF DETECTING DEFICIENCY OF VITAMIN A. G. W. ROBERTSON and J. YUDKIN, Brit. J. Ophth. **28**:556 (Nov.) 1944.

In this study, the instrument used was a modified and improved form of the adaptometer described by Hames (*Tr. Ophth. Soc. U. Kingdom* **48**:103, 1938). In the measurements of final rod threshold, groups of 3 or 4 subjects each enter a dark room directly from their work, without any previous light adaptation. After the subjects have been in the dark for thirty-five or forty minutes, the dark adaptation of each subject is measured by noting the minimal amount of light which can just be seen. The 3 or 4 subjects in each group are tested in turn and then tested a second time in the same order. The second value is taken as the measure of dark-adapting capacity. The following summary is made: Measurements of dark adaptation may be used to assess nutritional level with respect to vitamin A either by determination of the effects of the vitamin on dark adaptation or by comparison of the values for dark adaptation in various groups. The latter method, while not providing such conclusive evidence as the former, may sometimes give presumptive evidence of the relative nutritional status with respect to the vitamin, and for technical reasons it may be the only feasible procedure. Using the former method of measuring vitamin A lability, the authors showed that deficiency of vitamin A existed in a small group of laboratory workers and in a large group of Birmingham (England) factory workers. Of these workers, 147 who took vitamin supplements showed a statistically significant improvement in dark adaptation, while 188 controls showed no significant change. Three groups of school children showed no sign of vitamin A deficiency with this method.

By comparison of the values for dark adaptation in various other groups, it was shown that the Birmingham factory workers and a group of Sheffield factory workers had significantly poorer dark adaptation than the three groups of school children whose dark adaptation had been shown to be unaffected by vitamin A.

W. ZENTMAYER. [ARCH. OPHTH.]

THIAMIN FOR SCHOOL CHILDREN. S. MANGOLD, M. J. Australia **1**:34 (Jan. 1) 1945.

From observations on the increase in weight and height, days missed from school through illness, general conduct and school results over a period of five months of 38 children in the fourth, fifth and sixth grades, the author concludes that in areas where adequate food is given and normal care of their children is taken by parents there is no need for the indiscriminate use of thiamine.

GONCE, Madison, Wis.

THE IMPORTANCE OF THE VITAMIN B COMPLEX IN THE METABOLISM OF THE INFANT AND GROWING CHILD. F. W. SCHLUTZ, Rev. mex. de pediat. **13**:163 (Sept.-Dec.) 1944.

This is a review of many outstanding studies recently published on vitamins of the B complex, including several investigations carried on at the author's laboratory. Special stress is placed on interrelations between several of these factors and also on the synthesis of the vitamins of the B complex in the human body (colon); the symptoms of subclinical deficiencies, the reliability of various laboratory tests and the quantities of these vitamins necessary for optimal growth and development at different ages are also treated thoroughly.

The article does not lend itself to abstracting.

ABALLI, Habana, Cuba.

Hygiene; Growth and Nutrition; Public Health

OBSERVATIONS ON THE CHILD POPULATIONS, BIRTH AND INFANT DEATH RATES AND MEDICAL PERSONNEL IN CERTAIN COUNTRIES. JAMES B. GILLESPIE, Pediat. **26**:120 (Feb.) 1945.

The problems of relief and rehabilitation occasioned by World War II are the greatest in history. Prolonged dietary restriction, destruction of homes and sanitary facilities and the psychologic trauma of modern warfare have made definite and often permanent impression on the health of persons in civil populations. It is probable that infants, children and adolescents have been more adversely affected than other age groups.

To anticipate the nature and extent of problems in health and welfare of the young groups, the author made observations on the composition of populations as to age groups, birth rates and infant mortality rates and the rates of population per physician in certain countries. The studies involved countries in Western Europe, Scandinavia, the Balkans and the Far East. The proportion of infants and children in Far Eastern countries is generally greater than in other parts of the world; birth rates and infant mortality rates are high in the same areas. In Europe, the Balkans have the greatest proportion of total population under 5 years of age. The highest birth and infant mortality rates in Europe are in the Balkans. France and Belgium have the lowest birth rates in Europe, and the lowest infant mortality rates are in Norway and the Netherlands. The infant mortality rate in the United States is greater than in the last two European countries.

The ratio of population per physician is high in the Far Eastern countries. In the Netherlands East Indies it is 1 per 60,000, as compared with 1 per 743 in the United States. Yugoslavia, Bulgaria and Rumania have the highest ratios in Europe. In general, a close parallelism exists for most countries as regards infant mortality rates and ratios of population per physician.

It is believed that formulation of adequate relief plans for infants and children in the postwar period will be facilitated by those data which reflect the prewar health status and problems in younger groups.

AUTHOR'S ABSTRACT.

POSTWAR DEVELOPMENTS IN CHILD HEALTH STUDY IN GREAT BRITAIN. ALAN MONCREIFF, J. Pediat. **26**:189 (Feb.) 1945.

The past twenty-five years in Britain have seen the curious paradox of a steady improvement in the health of almost all children combined with a growing dissatisfaction with the medical services available for their care. This period has been one of great expansion in the child welfare services for the care of the young infant, and much original work has appeared from individual pediatricians on subjects of importance in the study of diseases of children. Yet these two streams of the medical care of the young have been flowing apart. The medical officers in the child welfare and school medical services have received little training in pediatrics, and hospital pediatricians were either not interested or not allowed to be interested in the care of the child in health.

Recent developments indicate that this unsatisfactory state of affairs is coming to an end. The new departments of child health in the universities of Durham and Liverpool and the promised development of an Institute of Child Health in London, together with the steady growth of existing departments in Edinburgh, Glasgow and Birmingham, all show that there is a new awakening of interest in the care of the child. It is likely that other universities in Britain will shortly announce developments on similar lines; it is in London, however, that the greatest interest is centered in possible developments. It has just been announced that Nuffield Foundation has allocated £100,000 ($400,000) for a chair of child health in the University of London and that it is proposed to create a postgraduate Institute of Child Health. This will be associated with the Hospital for Sick Children, Great Ormond Street, and the Obstetric department of the British Postgraduate Medical School at the Hammersmith Hospital of the London County Council. Among the special problems likely to be studied at such an institute may be included the following: (*a*) management of the premature baby, (*b*) nutrition and (*c*) physical therapy.

AUTHOR'S ABSTRACT.

Prematurity and Congenital Deformities

ANOMALIES OF THE SPEECH MECHANISM AND ASSOCIATED VOICE AND SPEECH DISORDERS. JAMES SONNETT GREENE, New York State J. Med. **45**:605 (March 15) 1945.

Greene, who is director of the National Hospital for Speech Disorders at 61 Irving Place, New York, read his paper before the annual meeting of the Medical Society of the State of New York March 9, 1944. He states that anomalies of the mouth and the larynx affect both voice and speech adversely and thus handicap the patient in his social and business life. Abnormalities of the tongue, tongue-tie and even elinguation, contrary to popular opinion, do not seriously affect speech. Clefts of the palate, on the other hand, do seriously affect speech even when repaired or treated by means of a fitted obturator. In either case subsequent training of speech is imperative. Tension on the muscles supplying the soft palate hold the nasopharynx open, and the voice is, therefore, of the rain barrel variety. After laryngectomy the voice may be produced by use of an artificial larynx or by training cervical muscles to produce the esophageal voice, i. e., by regurgitating swallowed air. It is possible through patient training to produce a voice that can be heard and understood in a room at conversational distance (4 to 6 feet [1 to 2.5 meters]) or over the telephone. It is preferable to develop a "substitute voice" rather than to depend on an artificial larynx, which up to now is a very imperfect affair.

VOORHEES, New York. [ARCH. OTOLARYNG.]

KLIPPEL-FEIL MALFORMATION. WILLIAM E. ALLEN JR., Radiology **44**:79 (Jan.) 1945.

The Klippel-Feil anomaly is characterized by absence or shortening of the neck, lowering of the hair line and limitation of motion of the neck, especially lateral bending. All or most of the cervical vertebrae may be fused. A large number of associated anomalies and deformities of the cervical vertebrae are commonly seen.

The author reports a case of this anomaly in a 24 year old soldier, whose sole complaint was a small tumor on the right shoulder which caused him some difficulty in carrying a pack. The following fifteen deformities and anomalies were seen in the roentgenograms: (1) elevation of the right scapula; (2) fusion of the first cervical vertebra and the occiput; (3) fusion of the bodies of the second and third cervical vertebrae; (4) fusion of the spinous processes of the second and third cervical vertebrae; (5) narrowing of the body of the fourth cervical vertebra; (6) spina bifida occulta of the bodies of the fourth and seventh cervical vertebrae; (7) bifid spinous process of the fifth cervical vertebra; (8) partial fusion of the bodies of the seventh cervical and first dorsal vertebra; (9) dorsal hemivertebra; (10) deformed bodies of the upper dorsal vertebrae; (11) kyphosis and scoliosis of the dorsal portion of the spine to the right; (12) right cervical rib; (13) fusion of the first and the second rib on the right; (14) rudimentary right twelfth rib, and (15) thinning of the left fifth rib posteriorly.

TEPLICK, Washington, D. C.
[ARCH. NEUROL. & PSYCHIAT.]

A CASE OF PARTIAL CONGENITAL HEMI-HYPERTROPHY. A. HUSE, J. Neurol., Neurosurg. & Psychiat. **7**:30 (Jan.-April) 1944.

Huse reports the case of a feebleminded man, aged 39, who showed enlargement of the entire left side of the body, involving both osseous and muscular tissues. The hypertrophied left side was weaker than the right. The condition was associated with signs of Recklinghausen disease. The author concludes that two congenital anomalies were present and that the mental deficiency was either idiopathic or secondary to the congenital anomalies.

MALAMUD, Ann Arbor, Mich.
[ARCH. NEUROL. & PSYCHIAT.]

Newborn

FETAL ERYTHROBLASTOSIS. ISRAEL DAVIDSOHN, J. A. M. A. **127**:633 (March 17) 1945.

Study of the Rh factor may be helpful in establishing the diagnosis of erythroblastosis in babies presenting the varying clinical syndromes of fetal hydrops, congenital anemia of the newborn or icterus gravis—especially when the jaundice is obstructive and suggests a possible congenital anomaly of the bile ducts.

In 90 per cent of cases fetal erythroblastosis is due to isoimmunization by the Rh factor, and demonstration of the characteristic distribution of this factor favors but does not establish the diagnosis. Finding of anti-Rh agglutinins in the mother further supports the diagnosis. Demonstration of these agglutinins requires special technics.

Hemolytic anemia is the initial pathologic state which initiates a sequence of interlocking changes giving rise to the other manifestations of the disease. Damage to the liver parenchyma is the fundamental pathologic change.

BAIRD, Wauwatosa, Wis.

THE DIAGNOSIS OF RH INCOMPATIBILITY, ESPECIALLY BY MICROSCOPIC APPEARANCES: ITS RELATION TO THE SYNDROME FORMERLY DIAGNOSED AS ERYTHROBLASTOSIS. MADGE THURLOW MACKLIN, J. Pediat. **25**:533 (Dec.) 1944.

"Rh incompatibility" is the term selected to designate the syndrome formerly called erythroblastosis and latterly called hemolytic anemia of the newborn. The need for a correct name for the syndrome is evident, since some authors call all cases of fatal or severe jaundice in the newborn, of hydrops or of congenital

anemia by the term erythroblastosis; others reserve this diagnosis for the excess hemopoiesis in the liver shown by some infants at birth; others use is to mean the reaction of a fetus with Rh-positive blood to anti-Rh antibodies from an immunized mother with Rh-negative blood.

The need of the fetus for an increase in red blood cells will be answered by the production of new red blood cells, whether the need arises through destruction of red blood cells by an antibody-antigen reaction, through loss of red blood cells by hemorrhage in the fetus or through anoxemia of the fetus, induced by lessened oxygen in the maternal blood or in the fetal blood. If the need for more red blood cells arises early in pregnancy, when the liver is still acting as a hemopoietic center, an excess of nucleated red blood cells will be present in the liver at birth. If the need arises late in pregnancy, when hemopoiesis is confined to the bone marrow, the liver may not show erythroblastosis, although nucleated red blood cells will be found in excess in the bloodstream. Thus, erythroblastosis is a symptom found in many fetal conditions and should not be used as synonymous with Rh incompatibility.

Since an antigen-antibody reaction similar to that found in Rh incompatibility may occasionally occur involving the A and B agglutinogens, with a similar response on the part of the fetus, the term "hemolytic anemia of the newborn" is not specific.

Proved cases of Rh incompatibility are those in which antibodies specific for the Rh antigen of the fetal red blood cells are present in the fetal blood.

Probable cases of Rh incompatibility are those in which the fetus possesses an Rh antigen which the mother lacks and also shows an anemia or jaundice or both if it lives; or in which the effects of destruction of red blood cells can be demonstrated in the organs at autopsy. Most of the gross and histologic criteria of so-called erythroblastosis are also present in persons with conditions other than Rh incompatibility. These are large spleen, liver, adrenals, heart and placenta; presence of nucleated red blood cells in the blood stream, in the liver and in the placental vessels; hypertrophy of the pancreatic islets, and persistence of the cytotrophoblast in the placental villi to term. Hence these conditions may be suggestive but not diagnostic of Rh incompatibility. The presence of iron in the liver as revealed by the prussian blue technic is not normal in fetal livers, as shown by examination of a series of fetuses varying in age from eight weeks to term. It indicates excess destruction of blood in the fetus, and one of the commonest causes of excess destruction of blood is Rh incompatibility. If iron in the liver at autopsy is coupled with the presence of incompatible Rh factors in mother and fetus, the diagnosis of probable Rh incompatibility may be made.

AUTHOR'S ABSTRACT.

ASPHYXIA NEONATORUM. HARRY R. LITCHFIELD, J. Pediat. **26**:279 (March) 1945.

A review of the literature dealing with asphyxia neonatorum and an evaluation of the methods used to combat the condition are given by the author.

He touches briefly on the causes of asphyxia and states that prematurity, trauma of labor, sedatives and general anesthetics in any amount increase the incidence of asphyxia. He agrees with Flagg that asphyxia neonatorum can be divided into three classifications—mild asphyxia, moderate asphyxia and asphyxia—and the article deals with the treatment of these conditions in a follow-up to the article written by Litchfield and Beilly in 1938. Case histories are cited, and the author concludes that in cases of mild asphyxia, alpha lobeline hydrochloride is indicated and that the sole administration of this drug is sufficient in most cases to overcome the condition. In severe attacks, alpha lobeline to initiate respiration should be administered as often as necessary, and this should be followed up by insufflation of oxygen, followed by a mixture of oxygen (93 per cent) and carbon dioxide (7 per cent).

The author endorses the method of administration outlined by R. A. Wilson in which alpha lobeline is injected into the umbilical vein and "milked" toward the infant. He states that while epinephrine has been useful in some cases, its effect on the circulatory system is too violent in conditions in which only a respiratory stimulant is indicated. Because of its transitory action and the fact that it exerts its effect only on the respiratory center, he states that alpha lobeline hydrochloride is the drug of choice in all types of asphyxia neonatorum.

The remainder of the article takes up in detail the effect of artificial respiration in asphyxia neonatorum, the use of the Drinker Respirator, the employment of mouth to mouth insufflation, the use of tracheal catheters and tubes, inhalators, pulmotors and resuscitators and finally a discussion of respiratory and vasomotor stimulants.

AUTHOR'S ABSTRACT.

OBSERVATIONS ON THE URINE OF THE NEW BORN INFANT. JOHN THOMSON, Arch. Dis. Childhood **19**: 169 (Dec.) 1944.

These observations were made on breast-fed infants of average weight in whom there was no clinical evidence of abnormality. In newborn infants there are wide fluctuations in the volume of urine and the output of urea and chloride from day to day. The results obtained show that in the first days of life the volume of the urine gradually increases, as does the frequency of micturition. The output of urea rises each day, but no parallel course is seen in the output of chloride. The specific gravity falls, while the p_H travels steadily to alkalinity.

KELLY, Milwaukee.

LOCAL PENICILLIN THERAPY IN OPHTHALMIA NEONATORUM. SORSBY and E. HOFFA, Brit. M. J. **1**:114 (Jan. 27) 1945.

The authors state that, unlike the sulfonamide compounds, penicillin remains effective in the presence of pus. It therefore has great possibilities for the local treatment of ophthalmia neonatorum in place of general sulfonamide treatment. Forty-seven infants in the ophthalmia neonatorum unit at White Oak (London County Council) Hospital were treated with penicillin. The concentrations began at 500 Oxford units per cubic centimeter and were gradually increased to 2,500 units; the doses were instilled at half hour intervals for the first three hours, then hourly for twenty-four hours and every two hours thereafter.

In a comparison of penicillin therapy and general sulfonamide treatment, the authors speak of the advantages of local treatment and avoidance of the danger of sensitization. At the same time, frequent irrigations are a trial to the infant and a considerable burden to the nurse. As the concentrations were increased from 500 to 2,500 units, there was an increasing proportion of satisfactory results. The authors conclude that in adequate concentration penicillin appears to be effective against all the common causal organisms of ophthalmia neonatorum, including the virus of inclusion blemorrhea.

It is likely that some forms of ophthalmia neonatorum respond more readily to penicillin than others, but on the whole the results are of the same order as those obtained with the sulfonamide compounds.

ARNOLD KNAPP. [ARCH. OPHTH.]

Acute Contagious Diseases

FACTORS INFLUENCING FALSE POSITIVE SEROLOGIC REACTIONS FOR SYPHILIS DUE TO SMALLPOX VACCINATION (VACCINIA). GRANT O. FAVORITE, Am. J. M. Sc. **208**:216 (Aug.) 1944.

Smallpox (vaccinia) vaccination followed by an accelerated or primary (nonimmune) cutaneous response is a newly recognized and important cause of biologic false positive serologic reactions for syphilis. The incidence of such reactions is at least 11 to 16 per cent.

The available evidence justifies the conclusion that an immune response to smallpox vaccination can be disregarded as a significant cause of a false positive serologic reaction for syphilis.

The false positive serologic reactions for syphilis are transitory. They appear within two weeks of the date of vaccination and disappear in most instances within two months. A few persist as extremely weak reactions as long as four months.

Typhoid (typhoid-paratyphoid vaccine) and tetanus toxoid immunizations have no bearing on the production of false positive serologic reactions for syphilis.

Suggestive data are presented to show: (*a*) that recently vaccinated persons who had a positive serologic reaction do not have a reactivation of their positive reactions following typhoid and tetanus immunizations five months later and (*b*) persons with false positive serologic reactions, when revaccinated for smallpox within seven months, may again present a weak serologic false positive response for syphilis, even though the second vaccinia reaction is of the immune type.

Positive serums stored in the refrigerator at 4 C. for seven months have a variable loss of titer. Such loss is not sufficient to be of differential diagnostic value.

HENSKE, Omaha.

MENINGOCOCCIC INFECTIONS; REPORT OF 43 CASES OF MENINGOCOCCIC MENINGITIS AND 8 CASES OF MENINGOCOCCEMIA. H. WEBSTER SMITH, LEWIS THOMAS, JOHN H. DINGLE and MAXWELL FINLAND, Ann. Int. Med. **20**:12 (Jan.) 1944.

Smith, Thomas, Dingle and Finland report on 51 patients with meningococcic infections admitted to the Boston City Hospital in the two year period beginning Sept. 1, 1940. Included among the 51 patients were 43 with meningitis and 8 with meningococcemia without clinical evidence of meningitis. The study was made in order to emphasize some of the less commonly recognized features of the clinical course, the results of laboratory tests and the therapy of meningococcic infections.

The authors noted from their case studies that one or more of the commoner features of meningococcic meningitis may be absent in a given case. It was possible to make a tentative diagnosis of meningococcic meningitis in almost every instance by examination of a smear of the cerebrospinal fluid or its sediment stained with Gram's method. However, the group II meningococcus should be carefully distinguished from the gonococcus, especially in cases in which the organism is recovered only from the blood.

The initial dose of a sulfonamide drug should be administered intravenously to patients with meningitis, even if they appear only moderately ill when first seen. All but 2 of the patients with meningitis who recovered showed objective signs of clinical improvement twenty-four hours or less after sulfonamide therapy.

The authors state that patients with a relative bradycardia, even though they may appear only moderately ill, should be observed for evidence of increased intracranial pressure. Lumbar puncture is of diagnostic value and should be employed as a therapeutic measure for the symptomatic relief of increased intracranial pressure. The presence of a normal sugar content of the cerebrospinal fluid following sulfonamide therapy or parenteral administration of dextrose was found to be in itself of no value in estimating the patient's clinical status. Pulmonary involvement was frequent in the patients with meningococcic meningitis and probably represented a local infection with the meningococcus, either alone or in association with other organisms.

There were 9 deaths among the 43 patients with meningococcic meningitis, but there were no fatalities among the 8 patients with meningococcemia.

GUTTMAN, Philadelphia.
[ARCH. NEUROL. & PSYCHIAT.]

SOME CLINICAL ASPECTS OF MENINGOCOCCIC INFECTION. F. DENNETTE ADAMS, Ann. Int. Med. **20**:33 (Jan.) 1944.

Adams discusses some of the less known or more frequently forgotten manifestations of meningococcic infection. Meningococcemia with acute meningitis, acute fulminating meningococcic septicemia (Waterhouse-Friderichsen syndrome), meningococcemia with arthritis and chronic meningococcemia are briefly considered. Meningitis may occur in any case which belongs in one of the last three groups, but the diagnosis must and can be made in the absence of symptoms and signs of meningeal involvement.

The author states that the response to sulfonamide drugs is little short of miraculous. Sulfadiazine at present is regarded as the drug of choice, with sulfathiazole a close second. He stresses the value of prompt and adequate sulfonamide therapy, the first dose being given intravenously. The condition of the patient is deemed the best guide to subsequent sulfonamide therapy. An adequate fluid intake is essential. Adams advises the use of meningococcus antitoxin for all patients who appear to be severely ill. Also, adrenal cortex extract and blood plasma may tide the patient over a period of so-called circulatory collapse.

GUTTMAN, Philadelphia.
[ARCH. NEUROL. & PSYCHIAT.]

DIAGNOSIS AND MANAGEMENT OF SEVERE INFECTIONS IN INFANTS AND CHILDREN: A REVIEW OF EXPERIENCES SINCE THE INTRODUCTION OF SULFONAMIDE THERAPY. III. MENINGOCOCCAL INFECTIONS. B. EXPERIENCES AT THE ST. LOUIS ISOLATION HOSPITAL. DAVID GOLDRING, RICHARD MAXWELL and ALEXIS F. HARTMANN, J. Pediat. **26**:15 (Jan.) 1945.

Two hundred and nine patients with meningococcic infections were admitted to the St. Louis Isolation Hospital between January 1942 and August 1943. The majority of cases was seen in the first six months of 1943.

A predilection of the disease for younger persons and for Negroes was noted. There was a fairly equal distribution between the sexes.

Classic signs of meningitis or meningococcemia were present in the majority of patients. Petechiae were noted in 155 instances.

The diagnosis of meningococcic infection was based on the recovery of meningococci from blood or spinal fluid or on the discovery of typical petechiae in patients with purulent but sterile spinal fluid.

A regimen of rather intensive sulfonamide chemotherapy was used, with satisfactory results. It is felt that the optimum blood level for sulfonamide compounds is between 20 and 40 mg. per hundred cubic centimeters until the patient shows definite clinical improvement. No unusual evidence of harm to patients from these blood levels was noted. A large volume of dilute alkaline urine is thought to be important in preventing hematuria. Sulfanilamide may be used to replace other sulfonamide compounds in the treatment of meningococcic infections if gross hematuria or suppression of urine occurs.

The newer sulfonamide compounds, sulfamerazine and sulfapyrazine, appear to be as effective as sulfadiazine in controlling meningococcic infections. For careful clinical studies of these drugs, the reader is referred to earlier reports in the medical literature.

The case fatality rate in this group of patients was 9.1 per cent. Half of the patients who died were moribund on their admission to the hospital. If these deaths are excluded, the case fatality rate is 4.5 per cent. The majority of patients who died after surviving more than twenty-four hours after admission to the hospital were elderly persons.

HARTMANN, St. Louis.

DIAGNOSTIC METHODS IN WHOOPING COUGH. NELLES SILVERTHORNE, VIVIAN ZACKS and EFFIE JENKINS, J. Pediat. **26**:155 (Feb.) 1945.

Eighty-seven children were examined for the presence of gram-negative bacilli in the nasopharynx. In addition to cultures of nasal mucus and cough plate cultures, each child was examined for Hemophilus pertussis. The results obtained were as follows:

1. Direct smear of nasal mucus revealed gram-negative bacilli in 80 per cent of patients with known whooping cough.

2. Cough plate cultures (taken in triplicate) were positive for H. pertussis.

3. The two culture methods used simultaneously were found to be superior in isolating H. pertussis to either one alone.

AUTHORS' ABSTRACT.

CULTIVATION OF MUMPS VIRUS IN THE DEVELOPING CHICK EMBRYO AND ITS APPLICATION TO THE STUDIES OF IMMUNITY TO MUMPS IN MAN. KARL HABEL, Pub. Health Rep. **60**:201 (Feb. 23) 1945.

The author was able to grow mumps virus in the yolk sac, amniotic sac and allantoic sac of the developing chick embryo. The chick embryo has been shown to be a suitable source of antigen for use in the complement fixation test and the diagnostic cutaneous test in man. A virus neutralization test in eggs has also been demonstrated. Within the limits of the collodion membrane technic, the virus has been shown to be greater than 340 millimicrons in particle size. This mumps virus is quite susceptible to the inactivating effects of heat, solution of formaldehyde ether and ultraviolet irradiation. Attempts to isolate virus from saliva of patients with mumps, by means of the chick embryo technic failed.

SANFORD, Chicago.

MENINGOCOCCIC MENINGITIS IN AN INFANT SUCCESSFULLY TREATED WITH SULFONAMIDE COMPOUNDS. L. VELASCO BLANCO, Arch. am. de med. **19**:6 (Jan.-March) 1943.

A case of a 4 month old girl with meningococcic meningitis is reported. She received sulfadiazine orally (0.20 Gm. per kilogram of body weight per day) and antitoxin intrathecally. An initial dose of sulfanilamide was also given intraspinally. The patient's general condition and the appearance of the spinal fluid improved rapidly. A morbilliform rash developed on the eighth day of treatment, which disappeared in twenty-four hours after the drug was discontinued. There were no sequelae.

ABALLI, Habana, Cuba.

IMMUNITY IN CHILDREN. J. F. FRANCO, Rev. mex. de pediat. **13**:178 (Sept.-Dec.) 1944.

The persistent absence of a positive agglutination reaction in 2 cases of typhoid fever is explained on theoretic grounds as another example of the deficient production of humoral antibodies in early life. In contrast, in infancy and early childhood cellular or tissue immunity is high. The author considers that such a fact should form the basis of future studies in the search for diagnostic laboratory methods for many diseases of infancy and early childhood.

ABALLI, Habana, Cuba.

Acute Infectious Diseases

PENICILLIN IN RAT BITE FEVER. W. A. ALTEMEIER, HARRY SNYDER and GERTRUDE HOW, J. A. M. A. **127**:270 (Feb. 3) 1945.

Two distinct types of rat bite fever are described. The more common type, due to Spirillum minus, is characterized by an incubation period of one to three weeks, a large maculopapular rash, local swelling and discoloration at the bite wound, regional lymphadenitis and response to arsenotherapy. The less common type, due to Streptobacillus moniliformis, is characterized by a shorter incubation period, a fine maculopapular or petechial rash, fewer local signs, arthritis, a blood culture positive for the Streptobacillus and little or no response to therapy with either sulfonamide compounds or arsenic. Three cases of the latter type are described. All 3 were cases of children with a history of a rat bite. All responded to therapy with penicillin injected intravenously and intramuscularly, although a child had a relapse after inadequate treatment. A comparison with the 17 proved cases previously reported in the United States indicates that penicillin is "an effective chemotherapeutic agent which shortens decidedly the course of the disease."

BAIRD, Wauwatosa, Wis.

PRIMARY COCCIDIOIDOMYCOSIS: A POSSIBLE PEDIATRIC PROBLEM. RALPH KUNSTADTER and ROBERT PENDERGRASS, J. A. M. A. **127**:624 (March 17) 1945.

It is now well recognized that the primary infection of coccidioidomycosis is much more common than the disseminated granulomatous form. A significant percentage of the infections of the primary type occur in children. The disease is endemic in Southwestern United States, but may present a diagnostic problem in any children visiting this area.

The acute stage, characterized by respiratory symptoms, erythema nodosum or multiforme, and arthritis occurs eight to twenty-one days after infection. Fever

ough and pleuritic pain are common. Eosinophilia is requent. The sedimentation rate is elevated and the eaction to the coccidioidin test positive. The subacute tage is characterized by changing pulmonary lesions evealed by roentgen examination. Loss of weight, ever and pulmonary symptoms may be observed. In he arrested or healed stage only nodular lesions are ound on roentgen examination. The prognosis is sually good.

Differentiation from tuberculosis may be difficult. A istory of possible exposure or of a characteristic acute pisode is of value. A positive cutaneous reaction to occidioidin or recovery of Coccidioides immitis from putum may help to establish the diagnosis.

BAIRD, Wauwatosa, Wis.

EXANTHEM SUBITUM (ROSEOLA INFANTUM). HARRY H. CLEMENS, J. Pediat. **26**:66 (Jan.) 1945.

Exanthem subitum (roseola infantum, pseudorubella, xanthem criticum, rose rash of infants and sixth disase) is a self-limited, acute illness of infancy characrized by an initial fever of three to five days' duration nd thereafter terminating in an erythematous, macular r maculopapular eruption with a predilection for the runk, neck and extremities. The disease is mildly conagious and is therefore considered infectious. The ause is unknown. In private practice cases occur ngly or in small groups; in institutions epidemics of he disease have been reported. Recovery is the rule s soon as the eruption appears. The prognosis is ways excellent, but harm may result from misdiagosing and overtreating the illness and from causing rief to the parents by unnecessarily quarantining the ome. Variations in the signs and symptoms of the lness occur frequently.

This malady is a definite clinical entity and is a disase entirely separate from any other eruptive fever infancy and childhood. It was first described miutely by Zahorsky in 1910 and for a second time in 913 and again concurrently by Veeder and Hempelman nd by Levy and Westcott in 1921.

In a twenty-four month period, May 1942 through lay 1944, 80 children with exanthem subitum from veral rural communities were examined. In our udy it was found that the disease occurred most freuently in infants of 6 to 18 months of age. Patients ere almost evenly divided between the sexes, 42 boys 2.5 per cent) and 38 (47.5 per cent) girls. There as a definite increase in the number of male patients the age period of 12 to 24 months. Exanthem subim apparently has a definite seasonal variation, tending occur most frequently in the spring months with an crease in October. Relatively few cases were obrved in the months of May, June, November and ecember.

In 57 cases (71.2 per cent) the onset was sudden with ild or few prodromal symptoms. In 52 of these the nset began with fever usually at night. In the maority of the cases no prodromal symptoms occurred ior to the fever. Generally speaking there were three ys of fever before the eruption occurred. About forty-ght hours prior to the appearance of the exanthem, erythematous enanthem of specks and streaks on the ft palate was noted in 70 cases (87 per cent). This anthem coincided with the height of the tubotympanitis nd the faucial and pharyngeal congestion. The period illness varied from five to nine days with the average riod at six days. Generally the convalescent stage tended to a period of forty-eight hours after the rash appeared. The demarcation between the acute and the convalescent stage of roseola infantum was sharp and crisis-like in 52 of the cases.

The leukopenia that is characteristic of the disease is most pronounced on the third day of fever. A progressive relative decrease of the polymorphonuclear cells and an increase in the lymphocytes occurred on the second, third, fourth and fifth days and was most pronounced on the fifth day.

No specific therapy is known or is necessary; hence treatment is entirely symptomatic. The pharyngitis tonsillitis and catarrhal otitis media clear up just as quickly without the use of sulfonamide compounds.

AUTHOR'S ABSTRACT.

MYOCARDITIS IN ACUTE INFECTIVE DISEASE. C. NEUBAUER, Arch. Dis. Childhood **19**:178 (Dec.) 1944.

This is a review of 200 cases of myocarditis occurring in patients with acute infectious diseases. There are pallor and some listlessness. Important signs are diminution of the first sound at the apex, changes in the character of the cardiac rhythm and some degree of enlargement. The blood pressure is usually low, and the electrocardiogram is an important aid in the diagnosis.

KELLY, Milwaukee.

PROPHYLAXIS OF TYPHOID WITH INTRADERMAL VACCINE. ANGEL ARGUDÍN GARCÍA, Bol. Soc. cubana de pediat. **16**:23 (Jan.) 1944.

In a series of more than 3,000 vaccinated children presented by the author there was not a single case of typhoid in spite of two epidemics in the neighborhood of the children. Ninety per cent of the patients were of low economic status.

The vaccine used was prepared from Cuban strains and strain no. 58 from Panama, of great antigenic power. The dose was 0.1 cc., given three times with an interval of a week. The flexor surface of the forearm was the area used. There was no local or systemic reaction.

KEITH, Rochester, Minn.

SALMONELLA SELANDÍA: REPORT OF SECOND CASE. A. CURBELO and J. M. MARTÍNEZ CRUZ, Bol. Soc. cubana de pediat. **16**:37 (Jan.) 1944.

The authors refer for the second time to the isolation of Salmonella selandía in man. The clinical picture in the present case corresponded to the summer gastroenteritis so common in Cuba.

The type was corroborated by the Salmonella center in New York for the study of Salmonella.

KEITH, Rochester, Minn.

AN INTERESTING OBSERVATION OF INFECTION WITH SALMONELLA. G. CARDELLE, A. CURBELO and J. A. MARTÍNEZ CRUZ, Bol. Soc. cubana de pediat. **16**:119 (April) 1944.

Until recent years it was maintained by laboratory workers that infections with Salmonella paratyphi A or B did not occur in Cuba. The authors describe a case of infection with S. paratyphi A in a 12 year old boy previously immunized with a typhoid-paratyphoid vaccine. Sulfathiazole, 3 Gm. daily (total, 37 Gm.), did not have a demonstrable influence on the course of the disease. The failure of the vaccine to protect the patient is explained by the relatively low immunogenic properties of strains of S. paratyphi A and the small number

of organisms contained in the commercial typhoid-paratyphoid vaccines.

KEITH, Rochester, Minn.

INFECTION WITH SALMONELLA CHOLERAE SUIS (AMERICAN TYPE). A. CASTELLANOS, A. CURBELO and J. A. MARTÍNEZ CRUZ, Bol. Soc. cubana de pediat. **16**:165 (May) 1944.

The authors refer to the statistical results of studies at the Salmonella center in New York which show the considerable frequency of salmonellosis of type C, chiefly that due to Salmonella cholerae suis. The frequency and importance of the infection appear to be similar in Cuba. Although the statistics are on a smaller scale, one difference is noted in almost all cases: In the north, S. cholerae suis of the type formerly known as "European" occurs, while in Cuba the "American," or biphasic, type, or the classic organism of Salmon and Smith is found. A case typical of the activity of this group is presented, and a résumé of the authors' experience with the material in general is given, with particular reference to observations on the disease in Cuba.

KEITH, Rochester, Minn.

Chronic Infectious Diseases

BIOLOGIC FALSE POSITIVE SPINAL FLUID WASSERMANN REACTIONS ASSOCIATED WITH MENINGITIS. VIRGIL SCOTT, FRANK W. REYNOLDS and CHARLES F. MOHR, Am. J. Syph., Gonor. & Ven. Dis. **28**:431 (July) 1944.

Scott, Reynolds and Mohr report 7 cases of confirmed false positive reactions of the spinal fluid of nonsyphilitic persons during the course of meningitis. In 3 cases the meningitis was of tuberculous, in 2 of meningococcic and in 2 of aseptic lymphocytic type. An additional case is included in which transfer of reagin from the blood to the spinal fluid may have occurred during an illness characterized by aseptic lymphocytic meningitis. These cases were from a series of 271 cases of meningitis of one of the types mentioned.

Unconfirmed positive Wassermann reactions of the spinal fluid were observed in an additional 20 cases of various types of acute intracranial disease occurring in nonsyphilitic patients. These cases were from a series of 200 cases of such diseases as pneumococcic, influenzal, streptococcic and staphylococcic meningitis; poliomyelitis; subarachnoid hemorrhage, and tumor of the cerebellopontile angle. The authors state that the positive Wassermann reactions could have been due to a technical error.

These observations indicate that, in view of the occurrence of false positive Wassermann reactions of the spinal fluid, the diagnosis of neurosyphilis based solely on the Wassermann reaction is unjustified in cases of meningitis and other types of acute intracranial processes until repeated tests performed after the condition has completely subsided demonstrate the continued presence of reagin. False reactions are usually short lived, for in 7 of the 8 cases reported in this series the reaction was transitory.

GUTTMAN, Philadelphia.
[ARCH. NEUROL. & PSYCHIAT.]

HEALED ASYMPTOMATIC MILIARY TUBERCULOSIS. KARL E. KASSOWITZ, J. Pediat. **26**:56 (Jan.) 1945.

An 8 year old boy reacted positively to tuberculin, and a roentgenogram showed healed primary tuberculosis; the hemogram and sedimentation rate were normal. Two years later, with a perfect school attendance record, on routine reexamination he presented a roentgenogram of evenly distributed healed, calcified miliary tuberculosis of the lungs. His general physical condition, hemogram and sedimentation rate were normal and washings from his stomach negative for Koch bacilli on inoculation into guinea pigs.

Three years later, the roentgenogram remained completely unchanged and gave the same picture of miliary tuberculosis.

AUTHOR'S ABSTRACT.

TUBERCULOUS PLEURISY WITH EFFUSION IN INFANCY. JANET B. HARDY and EDWIN L. KENDIG JR., J. Pediat. **26**:138 (Feb.) 1945.

Among 393 children under the age of 2 years infected with tuberculosis, there were 13 cases of tuberculous pleurisy with effusion. This represents an incidence of 3.3 per cent and seems to indicate that pleurisy with effusion is not a rarity. The incidence in 261 Negro children was 4.2 per cent and in 132 white children 1.5 per cent. The age incidence varied from 10 to 24 months. Only 1 of the patients was older than 2 years, and she had demonstrable tuberculous infection before the age of 2 years.

Unlike conditions obtaining in older children and adults, in every patient in this series an underlying tuberculous lesion was demonstrated by roentgenologic examination. These underlying lesions may be divided into two groups. There were 7 patients with only a primary tuberculous complex. All of these made an uneventful recovery. The 6 other patients had mediastinal tuberculosis complicated by tuberculous pneumonia; in 2 of these cavitation developed and both received pneumothorax therapy. There seemed to be a definite relationship between the pneumothorax therapy and the appearance of fluid in only 1 of these, and this patient had tubercle bacilli in her pleural fluid. In the other patient, fluid appeared before the pneumothorax was instituted.

Of the 13 patients in this series, 8 recovered with healing and calcification of the primary complex. Two patients later had the adult, or reinfection, type of tuberculosis, and 1 of these died with renal tuberculosis fourteen years later. Three other patients died of tuberculous meningitis. All 4 deaths occurred in Negroes.

Study of the literature suggests that pleurisy with effusion under the age of 3 years is a rarity. In 9 consecutive cases of tuberculous serofibrinous pleurisy taken from the diagnostic files of the Harriet Lane Home, the average age at the onset of the pleural effusion was 6½ years. The youngest patient having pleurisy with effusion to come to the attention of the authors was a 3 month old Negro girl with acute miliary tuberculosis, seen by Dr. Margaret Smith at Sydenham Hospital, Baltimore.

In each of the 13 cases in this study, the pleural effusion was found to occur early in the disease. In those cases in which the duration of the tuberculous process prior to the manifestation of the pleurisy was known it occurred within the first six months of the disease and in the majority of the cases within the first three months. In the 3 other cases of tuberculous pleural effusion occurring in the clinic, but not included in the study because the children were infected when over 2 years of age, the pleural effusion appeared in one month, seven months and six months respectively after infection.

As far as could be judged from this small series, the occurrence of serofibrinous pleurisy had no effect

the ultimate prognosis. As has been previously shown by other workers on pleurisy in older children and adults, the prognosis depends on the severity of the accompanying tuberculous process.

AUTHORS' ABSTRACT.

PRIMARY TUBERCULOUS INFECTION IN NURSES. MARC DANIELS, Lancet **2**:165 (Aug. 5); 201 (Aug. 12); 244 (Aug. 19) 1944.

This report analyzes data collected from one of the groups under observation in the Prophit Tuberculosis Survey, which was inaugurated in 1934.

The total number of nursing entrants to the survey was 3,764. All were student nurses drawn from two main groups of large general hospitals.

Nurses were given the Mantoux test, and roentgenograms were made shortly after entry into the preliminary training school. Of the 3,764 entrants 50.3 per cent had positive reactions to old tuberculin, 1 : 10,000 or 1 : 100,000 dilution; 30.5 per cent had positive reactions only to a 1 : 100 or 1 : 1,000 dilution; 19.2 per cent had negative reactions.

The rate of conversion to a positive Mantoux reaction in successive years of nursing training in the first year was 58.4 per cent and 78.3 per cent in the two hospital groups. Most of the subjects had no notable symptoms between the last negative reaction and the first positive one.

A study was made of the tuberculous morbidity of nurses who entered the survey before 1942 and whose chests on entry were shown by roentgenogram to be clear: The disease occurred in 33 of 452 nurses whose initial reaction to the Mantoux test was negative, and in 43 of 2,120 nurses whose initial reaction was positive.

The 33 cases arising in nurses whose reaction to the Mantoux test was negative on entry revealed the diversity of aspects of tuberculosis following primary infection in adults. In many cases it was difficult to determine whether the primary focus or a secondary infection was responsible for the lesion observed.

The evidence of this survey and the combined evidence of twenty other surveys show that the risk of development of tuberculosis following primary infection in young adults is a serious one.

The author suggests that a controlled method of antituberculosis vaccination is needed.

LANGMANN, New York.

TUBERCULOSIS OF RIGHT HIP WITH CHRONIC MILIARY INFECTION OF LUNGS. WILFRED SHELDON, Proc. Roy. Soc. Med. **37**:575 (Aug.) 1944.

In November 1943, a boy was admitted to the hospital for investigation, with pain in the right leg following a fall from a lorry. He was found to have limitation of all movements of the right hip joint, accompanied with pain. The reaction to the Mantoux test (1 : 1,000) was strongly positive. A roentgenogram of the chest showed typical miliary tuberculosis. Two months later roentgenologic examination showed no change in the lungs. There was no evidence of meningitis. The optic disks showed no tubercles, and gastric lavage yielded no tubercle bacilli. Two months later the child looked fit, his general condition was definitely improved and he was eating well. A roentgenologic examination of the chest showed no change, and a roentgenogram of the hip showed no improvement after the hip had been three months in a plaster spica cast.

WILLIAMSON, New Orleans.

Diseases of Blood, Heart and Blood Vessels and Spleen

COR BIATRIATUM TRILOCULARE: CASE REPORT. MARGARET M. GLENDY, R. EARLE GLENDY and PAUL D. WHITE, Am. Heart J. **28**:395 (Sept.) 1944.

A case of three chambered heart (cor biatriatum triloculare) with a tiny, rudimentary left ventricular pocket, attended by slight coarctation of the aorta in a boy aged 9 years is reported. The unusual clinical features, namely, absence of cyanosis and relatively good cardiac reserve until shortly before death, are discussed. The congenital abnormalities were complicated by a terminal infection (rheumatic [?]) and rapid dilation and failure of the heart. The clinical diagnosis of chronic rheumatic heart disease with involvement of the mitral valves was incorrect.

GIBSON, Chicago.

INCREASES IN THE PLASMA VOLUME FOLLOWING THE ADMINISTRATION OF SODIUM SALTS. RICHARD H. LYONS, SAMUEL D. JACOBSON and NOYES L. AVERY, Am. J. M. Sc. **208**:148 (Aug.) 1944.

The authors noted a significant increase in plasma volume in 14 subjects who received large amounts of sodium chloride or sodium bicarbonate.

The increase in the plasma volume was accompanied with an increase in venous pressure and body weight but was not accompanied with a proportional fall in the concentration of serum protein, hematocrit reading, hemoglobin concentration or red blood cell count.

Six subjects receiving 50 Gm. of sodium bicarbonate in forty-eight hours had a mean increase in plasma volume of + 400 ± 53.2 cc., or + 14.4 ± 1.54 per cent, with a mean increase in body weight of + 1.56 ± 0.358 Kg., or +2.33 ± 0.165 per cent.

Seven subjects receiving 40 Gm. of sodium chloride in forty-eight hours had a mean change in plasma volume of + 440 ± 35.5 cc., or + 15.6 ± 1.15 per cent, and a mean increase in body weight of 1.9 ± 0.41 Kg., or 3.16 ± 0.73 per cent.

HENSKE, Omaha.

MULTIPLE CONGENITAL ARTERIOVENOUS ANEURYSMS IN THE PULMONARY CIRCULATION. JOHN H. SISSON, GEORGE E. MURPHY and ELLIOT V. NEWMAN, Bull. Johns Hopkins Hosp. **76**:93 (March) 1945.

A case of multiple congenital arteriovenous aneurysms in the pulmonary circulation is presented. The diagnosis established by angiographic examination was confirmed at autopsy, and the pathologic changes are reported. The authors summarize the clinical picture in 6 cases reported in the literature. The usual symptoms are weakness, faintness, dizziness, dyspnea, pain in the chest and hemoptysis. The signs are cyanosis, clubbing of the fingers, often visible hemangiomas, bruit over the chest, polycythemia and roentgenographic evidence of localized opacity in the lung. The diagnosis can be definitely established by angiography. The treatment is pneumonectomy.

A brief discussion of angiographic technic and the physiologic effects of pulmonary arteriovenous communications is given. Angiographic examination has proved a useful procedure but may be dangerous in a patient with a circulatory shunt from the right to the left side of the heart.

A clinicopathologic analysis is made of 12 previously reported cases, together with the authors' case, in which death followed within one hour the intravenous injec-

tion of diodrast in a diagnostic procedure. A possible conclusion from the breakdown of these data is that the intravenous use of diodrast should be approached with caution in the case of a patient with hypertensive cardiorenal disease. FROM THE AUTHORS' SUMMARY.

INTRADERMAL USE OF CONVALESCENCE SERUM. ALAN BLOXSOM, J. Pediat. **26**:32 (Jan.) 1945.

A series of 40 persons, 2 adults and 38 children intimately exposed to measles, were given human measles immune serum intradermally. Doses used were 0.4 cc. amounts on successive days until 2 cc. was given. Thirty-four children and 2 adults did not have measles. Two children had uncomplicated measles before the course was completed. Two children had attenuated measles fourteen days after the inoculations, and in neither of these 2 children did any complications develop. It is believed at the present time that human measles immune serum has enough measles antigen available to produce an active immunity when this serum is given intradermally in at least the amounts suggested. The employment intradermally of human measles immune serum in the amounts suggested provides an economical use of this product. AUTHOR'S ABSTRACT.

TRAUMATIC RUPTURE OF THE SPLEEN. MAURICE S. MAZEL, J. Pediat. **26**:82 (Jan.) 1945.

Basing his report on a series of cases of traumatic rupture of the spleen correctly diagnosed and cured by promptly performed laparotomy, detailed histories of which are given, the author stresses several points of clinical value. Of these early diagnosis of a ruptured spleen is of prime importance, even when the symptomatology is not definite. Any trauma to the abdomen of a young child without external evidence of injury should be regarded as a case of potential rupture of the spleen irrespective of the blood count. Of course, signs of internal hemorrhage after an injury to the left side of the torso clinch the diagnosis. Even with profuse internal hemorrhage, the reduction of the red cells does not take place rapidly and may give rise to an erroneous diagnostic deduction.

Operative intervention is positively indicated, and laparotomy should be performed with the patient under spinal analgesia provided the proper blood pressure is maintained by transfusions. With spinal analgesia the spleen is easily reached and repaired if possible or extirpated when the damage is beyond repair. Other methods of securing anesthesia are of course available. With such management the mortality resulting from serious injuries of the spleen will be reduced to the minimum.

The author advances the concept that ruptured spleen in young children takes place by direct transmission of a trauma through the ribs. It is deemed a sound hypothesis to blame the ribs even without any visible injury to them, because in early life they are sufficiently resilient after being forced into splenic tissues to spring back into normal position.

But whatever explanation one may advance, the lives of such injured children can be saved only by prompt and skilful surgical intervention, after the patient has been placed in the best possible somatic condition.

AUTHOR'S ABSTRACT.

ELECTROCARDIOGRAPHIC STUDIES IN ASTHMATIC CHILDREN. H. T. ENGELHARDT and V. J. DERBES, J. Pediat. **26**:160 (Feb.) 1945.

In this paper, the authors attempt to evaluate the electrocardiographic manifestations of asthmatic children. The material consisted of 17 children with an average age of 9.3 years and an average duration of asthma of four and seven-tenths years.

The three conventional leads and the precordial leads CF_1, CF_2, CF_3, CF_4 and CF_5, with the exercise of accepted criteria, were employed.

The data tend to confirm results of a previous study to the effect that in children uncomplicated bronchial asthma is not a factor in the production of heart disease.

AUTHORS' ABSTRACT.

SIMPLE METHOD OF PREPARING POTENT BLOOD GROUPING SERA. A. S. WIENER, R. SOBLE and H. POLIVKA, Proc. Soc. Exper. Biol. & Med. **58**:310 (April) 1945.

Saliva from individual secretors of A and B substances was collected and autoclaved. The supernatant fluid was removed after centrifuging and then diluted with 4 parts of saline solution. Intramuscular injection of 0.2 cc. of the autoclaved saliva from groups A and B often stimulated a considerable increase in the iso-agglutination titer. The authors state that this method simplifies the large scale production of potent blood grouping serums. HANSEN, Galveston, Texas.

COARCTATION OF THE AORTA, OR STENOSIS OF THE ISTHMUS OF THE AORTA. JULIO A. JUNCO, Bol. Soc. cubana de pediat. **16**:142 (April) 1944.

A case of coarctation of the aorta in a white girl 12 years old is reported. This case was the third seen in eight years in the department of cardiology of the Infants Hospital at Habana. The report is followed by a full discussion of the pathology and symptoms with diagrams of the varieties of abnormalities encountered. KEITH, Rochester, Minn.

Diseases of Nose, Throat and Ear

THE ROLE OF CILIARY ACTION IN PRODUCTION OF PULMONARY ATELECTASIS, VACUUM IN THE PARANASAL SINUSES, AND IN OTITIS MEDIA. A. C. HILDING, Ann. Otol., Rhin. & Laryng. **52**:81 (Dec.) 1943.

Hilding briefly reviews some of the work done in the study of atelectasis and some of the physiology. In breathing, the lungs rise and contract, and the air passages shorten and become narrower. The diameter of the bronchi is said to vary as much as one third. The normal respiratory tract is lined throughout with a thin film of mucus, and this entire film is removed by ciliary action perhaps one to three times each hour and constantly replaced by the mucous glands. The total amount of mucous present at any time is small, but the respiratory mucus tends to span spaces, forming bubbles, diaphragms and threads. It has a certain tensile quality and can be dragged for a considerable distance. The cilia transport it readily and apparently can carry one hundred times the normal load without difficulty. The author, feeling that this mucus and the ciliary action might be a factor in the development of atelectasis and vacuum sinusitis, carried out several series of experiments. Using a short section of a chicken's trachea and respiratory mucus from a number of hens, he was able to demonstrate that the ciliary action carrying the plug of mucus along produced a negative pressure of 34 mm. of water within eighteen minutes. The greatest negative pressure in all the experiments was 35 mm. of water. He explains the development of the vacuum by the piston-like action

of the mucus plug in the trachea and feels that the steps leading to atelectasis are on the same basis. He says that the following circumstances combine to cause the occlusion: the force of the inspiratory flow of air, the changes in diameter and length of the bronchus, the bellows-like action of the involved lobe and the viscosity and the volume of the secretion. The occluding mass of mucus advances up the bronchus, causing a reduction of pressure in the lobe. The elastic tissue of the lobe reduces the size of the lobe as the pressure falls. The alveoli of neighboring lobes are carried forward by inspiratory air into the space which is relinquished by the affected lobe. The sliding movement of the lungs during respiration facilitates the shrinkage of the affected lobe and the enlargement of the neighboring lobes. These steps must be repeated many times with a succession of mucous plugs, each carrying along a volume of air somewhat on the principle of a mercury vacuum pump.

Hilding thought the same principle might explain the development of vacuum sinusitis and conducted experiments on dogs. Holes were drilled in the frontal sinuses of dogs, on both sides, of a size to hold an 18 gage hypodermic needle tightly. A needle on each side was connected with a water manometer. A second hole was drilled into the left side, a quantity of mucus was injected into the sinus and the needle was promptly closed. Negative pressure began to develop in the left sinus within a few minutes. Clinically vacuum sinusitis would develop when sufficient mucus reached the ostium to fill it completely and no incoming air could pass by. The pressure fell as the mucous mass was progressively dragged by nasal cilia and pushed by the sinus cilia through the ostium.

Some attempts were made to produce a vacuum in the middle ear by injecting mucus into the hypotympanum and the first part of the eustachian tube, but were unsuccessful. Nevertheless, the author believes that negative pressure in the middle ear is probably due to the force of ciliary action moving mucus down the tube.

M. V. Miller, Philadelphia. [Arch. Otolaryng.]

Treatment of Rhinorrhea and Otorrhea. Walter E. Dandy, Arch. Surg. **49**:75 (Aug.) 1944.

In rhinorrhea and otorrhea the cerebrospinal fluid is discharged from the nose and the ear respectively. Both conditions are due to a fistula connecting the cerebrospinal spaces, either the subarachnoid spaces or the ventricular system, with the exterior. The two great causes are fractures of the skull and openings created by operative procedures. Less frequent causes are erosions by tumors or infections and congenital abnormalities. Fortunately many fistulas heal spontaneously. The author reports 11 cases in twenty years. Continuing rhinorrhea and otorrhea nearly always demand surgical closure of the opening in the dura or the bone, preferably both. The indicated surgical operation is described. Two of the 11 patients treated died subsequently of intracranial infection.

Kaiser, Rochester, N. Y.

Roentgentherapy of Hemangioma of the Larynx in Infants. H. H. Kasabach and C. P. Donlan, J. Pediat. **26**:374 (April) 1945.

Kasabach and Donlan report 2 additional cases of hemangioma of the larynx in infants, with special reference to roentgenotherapy in the treatment of this condition. Laryngeal hemangiomas are believed to be congenital; they occur more frequently in males than in females, although the 2 cases reported in this article involved females. The usual symptoms are obstructive dyspnea, inspiratory stridor, a hoarse cry, a croupy cough and, rarely, blood-tinged mucus and gross hemorrhage. If there are pulmonary complications, fever is present. The diagnosis is made on a history of recurring, obstructive dyspnea and the laryngoscopic observation of a red or bluish subglottic mass. The presence of other hemangiomas on the body (in the absence of microscopic examination) and possibly a response of the laryngeal tumor to irradiation help to confirm the diagnosis. The dose which proved to be adequate in treatment of the tumors in the 2 cases reported was 1,200 r, delivered in less than three weeks. Preliminary tracheotomy is indicated. These cases are appended to the table of Seuhs and Herbut, who summarized the reported cases of hemangioma of the larynx in infants in 1940.

From the Authors' Summary.

Does Sinus Infection Affect Sinus Growth? Harry C. Rosenberger, Laryngoscope **55**:62 (Feb.) 1945.

It is known that early infection of the temporal bone prevents its subsequent pneumatization. Some have reasoned that infection may influence the growth and pneumatization of the sinuses similarly. Rosenberger explains why this is not so unless it be in isolated cases. He investigated 163 cases and observed "much greater frequency of infection in the more symmetrical antrum as compared with the low incidence of infection in the more variable frontal [sinus]." Several case reports are included.

Hitschler, Philadelphia. [Arch. Otolaryng.]

Contributions to Functional Pathology of the Ear: I. On Some Aspects of Treatment in Progressive Congenital Deafness. F. Kobrak, J. Laryng. & Otol. **58**:439 (Nov.) 1943.

Kobrak suggests that the activity of the intratympanic musculature is significantly changed in congenital deafness and that this change is due to a spastic condition of the muscles secondary to primary pathologic changes in the cochlear nerve. In this series of observations, treatment was directed toward altering the abnormal condition of the cochlear nerve and also that of the motor branches of the fifth and eighth nerves supplying the intratympanic muscles and the proprioceptive nerves of the muscles.

A report of 31 cases of otosclerosis and cochlear deafness is presented, in which the author did not systematically use strychnine and arsenic, as he feels that secondary degeneration of the nerve occurs after the administration of these drugs is stopped, giving poorer hearing than before treatment. It is reported that calcium and phosphorus are beneficial when used together. In this series, vitamin D was also given many times with calcium. Vitamin B was used in some cases because of the reported beneficial effect in spastic conditions in other regions.

Kobrak believes that it is important to eliminate toxic substances which are harmless in a normal person but dangerous to the hearing of the patient with slight congenital deafness. Among these substances are tobacco and the salicylates, a common offender being

acetylsalicylic acid. The danger of intense noise to the ear of the patient with otosclerosis is also emphasized.

He admits that it is not possible to alter the basic pathologic changes in congenital deafness. The patient's condition may be improved, however, by fenestrating the labyrinth, thus making a new pathway for sound waves, or by altering two variable factors, the pressure in the middle ear and the labyrinth and the activities of the intratympanic muscles and so of the damping apparatus. It is the latter factor that concerns him in the main, for he holds that the tympanic muscles operate at a key position for controlling normal and pathologic hearing and to some degree encourage the medical treatment of congenital deafness. The greatest promise is offered in combating the early stages of congenital deafness.

LeJeune and Steele, New Orleans.
[Arch. Otolaryng.]

High-tone Deafness in School-Children Simulating Mental Defect. Mary D. Sheridan, Brit. M. J. **2**:272 (Aug. 26) 1944.

Five children ranging between the ages of 9 and 14 years were suspected of being mentally defective. On examination they were found to have a high tone deafness. For this reason the author gives the following conclusions and recommendations:

The estimation of the hearing of children by pure-tone audiometric methods is highly skilled work. Every large school medical staff should possess at least one medical officer (preferably a recognized Certifying Officer already familiar with the normal standards of intelligence and scholastic attainment) who is adequately trained in audiometry and phonetics. Smaller authorities could send their cases for investigation to the larger centers.

"The hearing of all children over 7 years old who show persistent defects of articulation should be investigated by this trained medical officer. The cooperation of other school medical officers, speech therapists, and teachers in referring cases is essential.

"No child with persistent defective articulation should be certified as mentally defective on the results obtained from tests involving language without an investigation of the hearing.

"Accurate diagnosis of high-tone deafness is already possible. The problems of its aetiology and treatment (medical and educational) are matters urgently needing consideration."

Birdsong, University of Virginia.

An "Explosive" Outbreak of Haemolytic Streptococcal Tonsillitis on an R. A. F. Station. Thomas S. Wilson, Brit. M. J. **2**:275 (Aug. 26) 1944.

In a total camp of 14 officers and 351 airmen, 89 airmen were affected during an outbreak of acute hemolytic streptococcic tonsillitis. The patients were acutely ill, showing distinct local and general reactions. The tonsils were red and edematous, with patches of exudate. In many cases the cervical glands were enlarged and tender, and in those patients without tonsils there was a diffuse pharyngitis. The temperatures ranged as high as 104 F. The response to the sulfonamide compounds was not as dramatic as might have been hoped. In many cases there was a recrudescence of pyrexia around the tenth day. The blood sedimentation rates were almost invariably much raised and remained increased for four to five weeks. Convalescence was rather prolonged, being from three to four weeks. There were 2 cases of otitis media, 1 of acute carditis and 2 of arthritis among the complications. Material swabbed from the throats of a number of patients on culture grew a hemolytic Streptococcus which belonged to the Lancefield group A and was serologically type 9. On investigation it was found that one of the cooks, who harbored group A type 9 hemolytic streptococci, had an infection of the upper respiratory tract and just before this epidemic had been in charge of preparing and distributing milk.

There was no correlation between groups of men who were billeted together, but there was a strong correlation between men eating in the same mess hall; hence it was concluded that this was a food-borne infection. This epidemic is similar to an outbreak of streptococcic sore throat in an American army camp in that (1) both outbreaks were food-borne infections and (2) in both epidemics patient to patient infection was minimal.

Birdsong, University of Virginia.

Acute Sinusitis and Technic of the Antrum Washout. James Crooks, Proc. Roy. Soc. Med. **37**:575 (Aug.) 1944.

The author presented the cases of 5 children suffering from inflammation of the accessory nasal sinuses and illustrated complications which may arise from the disease. He also demonstrated the technic of lavage of the antrum of a young subject under local anesthesia.

Williamson, New Orleans.

Penicillin Therapy in Hemolytic Streptococcus Pharyngitis and Tonsillitis. Norman Plummer, Dorothy Duerschner, Harold Warren, Francis Rogliano and Ruell Sloan, J. A. M. A. **127**:369 (Feb. 17) 1945.

Forty-five cases of pharyngitis and tonsillitis due to group A (Lancefield) hemolytic streptococci were studied by the authors.

Twenty-eight patients received penicillin in doses of 15,000 units every four hours for periods of twenty-four hours to six days. Symptomatic relief began in eight to twelve hours. Cultures of materials taken twenty-four hours after penicillin therapy was instituted were almost always negative for streptococci. After discontinuance of the drug, the frequency of reappearance of the organisms was inversely proportional to the length of time the drug was given. Relapses occurred in 4 of 9 patients treated for less than four days. None of 10 patients treated for six days had relapses, but in 1 a streptococcic sinusitis and pneumonia subsequently developed.

Of 11 control patients treated with sulfadiazine, out of 8 who had many streptococci on original culture only 1 had a culture negative for streptococci.

Of 6 control patients without specific therapy, the 5 who had many organisms on original culture continued to have cultures positive for streptococci throughout the period of acute illness.

Baird, Wauwatosa, Wis.

Gigantic Cholesteatoma in a Child. Roberto Machado Ortega, Bol. Soc. cubana de pediat. **16**: 130 (April) 1944.

A case of a huge cholesteatoma in a 9 year old boy is described. The cholesteatoma had destroyed, by expansion, all the right external auditory canal, the anterior wall of the mastoid and aditus and had invaded the entire region of the mastoid up to the lateral sinus. The report is followed by a discussion of the pathologic

natomy, pathogenesis, symptoms and treatment. The uthor asks, "Is there a cholesteatoma diathesis?" and iscusses the two types of the lesion, primary congenital holesteatoma and the type associated with or due to nfection.

KEITH, Rochester, Minn.

Diseases of Lungs, Pleura and Mediastinum

TUDIES ON PRIMARY ATYPICAL PNEUMONIA: II. OBSERVATIONS CONCERNING THE RELATIONSHIP OF A NON-HEMOLYTIC STREPTOCOCCUS TO THE DISEASE. LEWIS THOMAS, GEORGE S. MIRICK, EDWARD C. CURNEN, JAMES E. ZIEGLER JR. and FRANK L. HORSFALL JR., J. Clin. Investigation **24**:227 (March) 1945.

Nonhemolytic streptococci, comprising a homogenous roup and belonging to a single immunologic type, have een isolated from the lungs and sputums of patients ith primary atypical pneumonia. Specific antibodies irected against this species of streptococcus have been emonstrated in the convalescent serum of patients with rimary atypical pneumonia by means of a number of erologic technics. With few exceptions, such antiodies were not demonstrable in the serum of those atients during the acute phase of the disease, in the erum of patients with other diseases nor in the serum f normal persons. These results suggest the possiility that this streptococcus may be implicated in the athogenesis of primary atypical pneumonia.

In the preceding paper of this series (page 209), not bstracted, there is presented a comprehensive study of 06 patients with primary atypical pneumonia, with a eview of the literature on this disease and a variety of linical and laboratory observations correlated with the esults of other studies.

GUEST, Cincinnati.

GENERALIZED OBSTRUCTIVE EMPHYSEMA IN INFANTS. WALDO E. NELSON and LAWRENCE W. SMITH, J. Pediat. **26**:36 (Jan.) 1945.

Acute and chronic respiratory disturbances in which he characteristic clinical manifestation is an expiratory ype of dyspnea associated with generalized emphysema re not uncommon in the first few years of life. While rom a clinical standpoint the cases which fall in this ategory have certain features in common, they do not epresent a single entity.

The respiratory obstruction is principally in the distal r smaller bronchioles, and clinically such diagnostic erms are employed as bronchiolitis, capillary bronchitis, neumonitis, interstitial pneumonia, and in certain instances aspiration pneumonia. There is, as a rule, obtruction to both aspiration and expiration, but the difficulty in expiration is the more prominent and air is trapped in the alveoli, producing emphysema.

There are, of course, marked variations in the degree of obstruction as well as in the nature of the obstructing lesion, so that not only does the degree of emphysema vary but in the same case there are frequently areas of atelectasis as well as of emphysema.

Clinically there are certain similarities to asthma, but in contrast to the usual relatively short duration and self-limited course of the average attack of asthma even the acute forms of obstructive emphysema in infants tend to persist for a week or so and many of them for a much longer period. Furthermore, while asthma is perhaps the most frequent cause of obstructive emphysema in older children, it is relatively uncommon in the first year or two of life, when the conditions under consideration characteristically occur.

While no single description is applicable to all cases of obstructive emphysema, there are certain features which they have in common. There are an increased respiratory rate and noticeably decreased respiratory excursions associated with a utilization of the accessory muscles of respiration. The latter results in an indrawing at the suprasternal notch and at the lower margin of the thorax. The indrawing at the upper and lower ends of the sternum and of the thorax is not so pronounced as in cases of severe laryngeal or tracheal block, in which the obstruction is principally inspiratory in type. In contrast to laryngeal obstruction, there is usually no hoarseness or stridor, and in contrast to asthma, frequently no audible wheezing. Cyanosis depends on the degree of the obstruction. The percussion note is hyperresonant except over localized areas of consolidation, and the respiratory murmur is characterized by a prolongation and usually a roughening of the expiratory phase. There may or may not be fine or medium rales. Roentgenographic and fluoroscopic examinations of the chest are of great help in confirming the diagnosis. On the roentgenogram, the diaphragm is seen to be low and flattened, the ribs farther apart than usual and the pulmonary fields less dense. There may or may not be stringy or patchy areas of density or even relatively large areas of atelectasis. Of even more significance, however, is the fluoroscopic evidence of the greatly restricted excursion of the low and flattened diaphragm. In the cases of more severe disturbance the excursion is so slight that it appears to be little more than a quivering movement. Furthermore, there may be a slight increase in the horizontal diameters of the chest during expiration suggesting that the emphysematous lungs are simply being forced into a different position rather than being emptied of any significant quantity of the trapped air.

In our experience this type of respiratory disturbance is far from uncommon and, while the majority of the infants observed have had an acute, self-limited course unaffected by the sulfonamide drugs and strongly suggestive of being the infantile counterpart of influenzal (virus) pneumonitis or of so-called primary atypical or viral pneumonia, there have been a variety of pathologic conditions which have been responsible for dyspnea in association with obstructive emphysema. These have included aspiration of amniotic contents during birth, cystic fibrosis of the pancreas, atypical bronchopneumonia, laryngotracheobronchitis, miliary tuberculosis, aspiration of zinc stearate powder and chronic passive congestion secondary to a congenital heart lesion.

AUTHORS' ABSTRACT.

VIRUS PNEUMONIA: A RÉSUMÉ AND A THERAPEUTIC SUGGESTION. HERMAN J. WOLFF, Minnesota Med. **28**:43 (Jan.) 1945.

Treatment of virus pneumonia has not afforded the clinician much opportunity for a display of skill. For the most part, it may be briefly summarized as supportive therapy with the relief of cough a predominant feature. The sulfonamide drugs are certainly not of value but may be used empirically until an accurate diagnosis is made. After the accurate diagnosis of virus pneumonia the sulfonamide drugs may be either discontinued or continued in decidedly reduced amounts because of their bacteriostatic value for the prevention of complications. However, the author feels that a review of the literature has given convincing evidence that injections of convalescent serum may control virus pneumonia or shorten its term. He has tried this form

of therapy for his patients, and the results have indicated that further use of convalescent serum is certainly worth while.

STOESSER, Minneapolis.

PLEURAL AND PULMONARY SUPPURATION TREATED WITH PENICILLIN. J. E. H. ROBERTS, OSWALD S. TUBBS and MICHAEL BATES, Lancet **1**:39 (Jan. 13) 1945.

Penicillin appears to lower the incidence of infection in cases of traumatic hemothorax.

Twelve patients with acute pyogenic empyema were given local treatments with penicillin. Sterilization is usually obtained readily, but aspiration and intrapleural injection of penicillin alone result in so much pleural thickening that operative treatment is required as soon as thick pus forms. Penicillin administered intrapleurally will play its most important role in cases in which diagnosis is made at an early stage, when the fluid is still thin and localization has not occurred. This applies particularly in cases of empyema of streptococcic origin with the pneumonic process remaining active, especially in children or in aged persons.

Penicillin administered intrapleurally is a valuable agent in eradicating secondary infection from tuberculous pleural effusions.

The systemic administration of penicillin in cases of pulmonary suppuration requires much further investigation. One patient with thoracic actinomycosis showed dramatic improvement.

LANGMANN, New York.

PULMONARY HAEMOSIDEROSIS. D. REYE, M. J. Australia **1**: 35 (Jan. 13) 1945.

The author reports the case of a young child in whom anemia of unknown causation over a period of fourteen months ended in death by respiratory embarrassment due to an abundant and extensive foreign deposit in the lung parenchyma. This foreign deposit was composed of hemosiderin granules, large and small, mainly enclosed within large histiocytes but also lying free in the air sacs. Together with this, there was unchanged hemoglobin, and in some air sacs there were collections of undestroyed erythrocytes. The pulmonary capillaries were dilated except where pressed on by densely filled alveoli, but in these channels and in the larger vessels no histologic peculiarities were obvious. Apart from a proliferation of normoblasts, the marrow from the femur was normal. The clinical course and histologic examination of the heart excluded primary cardiac disease as the explanation of the condition.

GONCE, Madison, Wis.

THE PROGNOSIS OF BRONCHIECTASIS IN CHILDHOOD (ABSTRACT). R. WHITE FRANKLIN, Proc. Roy. Soc. Med. **37**:576 (Aug.) 1944.

In his abstract the author gives a review of the prognosis of 24 cases of bronchiectasis observed both clinically and roentgenologically for periods ranging between four and twelve years. He classifies the patients into three groups: (1) those "absolutely well"; (2) those "delicate," that is, well for the most part but requiring special care and (3) "invalids," who by reason of poor general health or constant cough and raising of sputum cannot live a normal life. Of the 24 patients 15 are well, 4 are delicate and 5 are invalid. Two tables accompany the report. In table 1 the cases are arranged in the order of probable duration of the disease; in table 2 is presented a breakdown of the cases according to the three classes and according to the dilation, the number of lungs involved and the presence of clubbing and of sinus infection. From the study of these cases it was found that the age, the type of onset and the duration of the disease do not directly affect the prognosis.

WILLIAMSON, New Orleans.

SURGICAL TREATMENT OF BRONCHIECTASIS IN CHILDREN. R. S. PILCHER, Proc. Roy. Soc. Med. **37**:57[illegible] (Aug.) 1944.

The author discusses at length the surgical treatment of bronchiectasis in children and accompanies the report with three tables. Table 1 presents a résumé of the surgical treatment of bronchiectasis in children in the surgical unit, University College Hospital; table 2 shows the mortality and morbidity of surgical treatment, and table 3 shows the results of operation in 28 completed cases of bronchiectasis.

WILLIAMSON, New Orleans.

BRONCHIOLITIS IN CHILDREN. G. H. NEWNS, Proc. Roy. Soc. Med. **37**:580 (Aug.) 1944.

Acute bronchiolitis until very recently was called acute capillary bronchitis. Another name was acute suffocative catarrh, because of the obstructive dyspnea which is so characteristic a symptom. There is a considerable difference of opinion as to its existence as a distinct disease. It was once a much commoner disease than it is today. The diminution in incidence may, of course, be largely due to the improvement in the general health of the young infant and in his medical care. The commonest causes of acute bronchiolitis are (1) influenza, (2) measles and (3) pertussis. Bronchiolitis may be divided into (1) the catarrhal type and (2) the mural type, which may be subdivided into (*a*) simple, (*b*) proliferative and (*c*) destructive.

Before discussing the two types, the author describes fully with plates the histology and anatomy of the bronchiole. He then takes up the following subjects and discusses each: (1) causes of difference in reaction, (2) morbid anatomy, (3) clinical features, (4) diagnosis, (5) treatment and (6) etiology.

WILLIAMSON, New Orleans.

KEROSENE AND BENZENE PNEUMONIAS IN CHILDREN. C. PELFORT, J. CASSINELLI and J. M. PORTILLO. Arch. de pediat d. Uruguay **15**:557 (Oct.) 1944.

The authors report 21 cases of aspiration of benzene, kerosene and other allied hydrocarbons and review the literature on this subject. The ages of patients reported on varied from 6 to 43 months. The immediate symptomatology is characterized by expectoration, vomiting, cyanosis, nervousness to somnolence, tachypnea and respiratory irregularities, fever and tachycardia. Roentgenographic studies were made in 19 cases, and abnormalities were noted in 18 cases. Leukocytosis, with a count up to 20,000, was found in several cases, but no conclusions were drawn. In all cases prompt therapy was instituted. No fatalities were reported.

The authors discourage the practice of gastric lavage, oxygen inhalations and artificial respiration in these cases and advise only symptomatic measures, with the use of sulfathiazole against secondary infections.

PLATOU, New Orleans.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

INFECTIOUS GASTROENTERITIS: EPIDEMIOLOGIC AND LABORATORY STUDY. EDWARD C. ROSENOW, Am. J. Digest. Dis. **11**:381 (Dec.) 1944.

A study of a series of outbreaks of gastroenteritis resembling, and usually erroneously considered to be, food poisoning is reported.

Streptococci or diplostreptococci with which diarrhea and lesions in the gastrointestinal tract have been produced among animals have been isolated consistently by special methods from the nasopharynx, stools and blood of patients, from the water supply of patients and from the air of rooms occupied by persons with gastroenteritis. Ordinary mediums in general use usually did not suffice for initial isolations, which must be done in dextrose brain broth. Escherichia coli was isolated rarely from water supplies, and Shigella dysenteriae was never isolated from water supplies or stools of patients with gastroenteritis. The total bacterial counts as determined by plating in agar were low in drinking water yielding the streptococci or diplostreptococci at the time of outbreaks. Chlorination sufficed to render the water of the city free from the streptococci and the diplostreptococci at the water plant but did not suffice at the periphery, where cases of the disease occurred. Mild contamination with the diplostreptococci of the water from wells 500 feet (150 meters) deep, while seemingly responsible for isolated sporadic cases, was never sufficient to cause a major outbreak except as it led to contamination of articles of food, such as milk (outbreak A). Peripheral "autogenous" contamination of the water supply through "Flushometer" toilet valves or other sources of fecal contamination was responsible for at least two major outbreaks (outbreaks B and C). In one household recurring outbreaks of gastroenteritis were traced to back siphonage through the under water level inlet of a bathtub.

A filtrable infectious agent resembling a virus developed in chick embryo medium cultures of the Streptococcus and Diplostreptococcus of ulcerative colitis. With this agent the disease picture of gastroenteritis was mainly produced on several successive passages through animals, after which symptoms and lesions of encephalitis supervened. As this occurred, the incidence of isolations of streptococci progressively decreased.

The Streptococcus and Diplococcus isolated in this study were closely related to the Diplostreptococcus of ulcerative colitis (Bargen). Streptococcus antigen was demonstrated in the skin of patients by intradermal injection of the euglobulin fraction of the ulcerative colitis antistreptococcus serum, in the serum of patients during the acute stage of the disease and in washings from the air during epidemics by the precipitation reaction with the ulcerative colitis antistreptococcus serum. Specific agglutinins for the Streptococcus and Diplostreptococcus were demonstrated in the serum of patients during convalescence. AUTHOR'S SUMMARY.

ROENTGEN FEATURES OF CHRONIC TUBERCULOUS PERITONITIS. JAMES J. MCCORT, Arch. Surg. **49**:91 (Aug.) 1944.

The clinical diagnosis of tuberculous peritonitis is usually difficult. There are a variety of clinical manifestations, and on physical examination the patient generally reveals a distended abdomen. Soft doughy masses may be palpable within the abdomen. These are due to infiltration and thickening of the omentum and its contraction into lumps by the formation of adhesions. The author describes 6 cases of tuberculous peritonitis, in 3 of which the preoperative diagnosis was suggested by the roentgenographic appearance of the large and the small bowel. The diagnostic points are:

1. A low grade ileus with a varying amount of intra-abdominal fluid will be seen on the plain roentgenogram.

2. The barium sulfate enema will show the large bowel to be in a fixed position.

3. The enema of the small intestine will as a rule disclose rapid passage of the barium sulfate. The loops of the intestine are bound together, and the bowel is shorter than normal. KAISER, Rochester, N. Y.

MECKEL'S DIVERTICULUM. WILLIAM L. SIBLEY, Arch. Surg. **49**:156 (Sept.) 1944.

Some type of Meckel's anomaly is present in approximately 4 per cent of all newborn infants, though the rate of occurrence in adults is given as from 1 per cent to 3 per cent by different authorities. Meckel's diverticulum may be present throughout the life of a person and yet cause no symptoms, but, owing to the serious consequences of the pathologic conditions to which it is subject, it is always a source of great potential danger. The symptoms are discussed in detail, and a classification of the various types is described. The treatment of Meckel's diverticulum is surgical. It must be directed toward relieving the symptoms produced by the diverticulum. The operation must include excision of the diverticulum.

KAISER, Rochester, N. Y.

EPIDEMIC DIARRHEA, NAUSEA AND VOMITING OF UNKNOWN CAUSE. HOBART REIMANN, JOHN HODGES and ALISON PRICE, J. A. M. A. **127**:1 (Jan. 6) 1945.

An outbreak of a mild epidemic disease characterized by anorexia, malaise, diarrhea, nausea and vomiting is described as occurring in Philadelphia and being similar to outbreaks reported elsewhere. It is not known whether this syndrome is related to epidemic diarrhea of the newborn. Apparently the disease is not related to food or water or caused by any known pathogenic bacteria. A filtrable virus affecting the respiratory, the gastrointestinal or the central nervous system is suggested as the cause. BAIRD, Wauwatosa, Wis.

ABDOMINAL PAIN IN CHILDREN. JOSEPH BRENNEMANN, J. A. M. A. **127**:691 (March 24) 1945.

Dr. Brennemann emphasizes the difficulties and hazards encountered in the diagnosis of abdominal pain in children. His concise description of the causes of pain, first the obstructions and then the infections, cannot be properly abstracted but must be read in its entirety. BAIRD, Wauwatosa, Wis.

ABDOMINAL PAIN IN CHILDREN DUE TO ALLERGY. BRET RATNER, J. A. M. A. **127**:696 (March 24) 1945.

Abdominal pain in children may be due to allergy. This pain may be difficult to diagnose and may simulate the pain of other disorders. Mechanisms to explain the establishment and manifestations of sensitization to food are suggested. Allergy of the gastrointestinal tract without cutaneous or pulmonary symptoms usually does not produce diagnostically valuable cutaneous reactions. The diagnosis rests on history, ingestion tests and the response to epinephrine or atropine. Roent-

genologic evidence of pylorospasm, delayed gastric emptying, hypertonicity and hyperperistalsis of the intestine are of value in diagnosis. Treatment includes the elimination of the offending foods, the use of them in "allergenically denatured" forms or the building up of a tolerance for them.

BAIRD, Wauwatosa, Wis.

PURULENT PAROTITIS IN THE NEWBORN. HEYWORTH N. SANFORD and IRENE SHMIGELSKY, J. Pediat. **26**:149 (Feb.) 1945.

Five cases of purulent parotitis in newborn infants in a five year period are reported, making a total of 62 reported cases. However, it is believed that this disease entity occurs more frequently than reported cases indicate. The organism cultured in every instance was a hemolytic Staphylococcus aureus. Two of the infants were premature; 2 were small babies and 1 weighed more than the usual newborn infant. One of the infants was syphilitic; antisyphilitic therapy was instituted for it. The course and symptoms were typical in all instances. An unexplained rise in temperature from 101 to 104 F. occurred on the seventh or eighth day of life, and within twenty-four hours a swelling of the parotid gland was noted with associated heat and redness. There were anorexia and some loss of weight. Leukocytosis, with a white cell count of 18,000 to 40,000, was noted for a few days with polymorphonuclear cells averaging from 65 to 80 per cent. The gland rapidly increased in size and became fluctuant in three to four days, after which it was incised. In 1 infant, the right parotid and left cervical lymph nodes were involved; cultures of the pus revealed the primary organism. Recovery occurred in one to two weeks. Sulfathiazole was given by mouth, 2 grains (0.13 Gm.) per pound (453 Gm.) of weight in twenty-four hours in four doses and continued as long as there was any drainage or until the leukocyte count had fallen noticeably. Healing was prompt, leaving a small imperceptible scar.

SHMIGELSKY, Chicago.

THE TIME FACTOR IN THE PRODUCTION OF GASTRIC LESIONS ON LOW CALCIUM DIETS. T. F. ZUCKER and B. N. BERG, Proc. Soc. Exper. Biol & Med. **57**:1 (Oct.) 1944.

Previous work of the authors (*Proc. Soc. Exper. Biol. & Med.* **53**:34 1943) revealed that in rats maintained on a low calcium diet for four weeks gastric lesions developed which occurred only in the antrum, the nonacid, mucus-secreting regions of the glandular portion of the stomach. Return to normal calcium levels in the diet prevented the lesions. In the present experiment, the same diet, containing 0.017 per cent calcium and 0.041 per cent phosphorus, was fed for eight weeks, at the end of which time the same types of change were observed except that the gastric lesions were larger and more confluent and more central craters contained blood clots and often bled, but the lesions remained superficial and did not tend to perforate. Control animals had no such abnormality (there were 10 or 12 animals in each group). The underlying cause of this abnormality was not determined, but this dietary regimen tended to bring about a generalized tendency to bleeding.

HANSEN, Galveston, Texas.

HYPOPHOSPHATEMIC RICKETS WITH GLYCOSURIA, KETONURIA AND ACIDOSIS (DE TONI–FANCONI SYNDROME): A CLINICAL CASE WITH POSTMORTEM STUDIES. A. J. ABALLÍ, RENÉ MONTERO, A. ESCOBAR ACÉS and JUAN JIMENEZ, Bol. Soc. cubana de pediat. **16**:3 (Jan.) 1944.

The authors review the literature and present a case, the first reported in Latin America, of a 2 year old white boy with a history of remittent fever (temperature about 101 F.), abdominal distention and constipation since the age of 6 months. Later, polydypsia, polyuria and glycosuria, anorexia and one tonic convulsion occurred.

On admission the boy was irritable, dehydrated and undernourished. The height was 73 cm. There was so-called capus quadratum, with patent anterior fontanel and rachitic rosary. Scoliosis, abdominal distention and hepatomegaly and splenomegaly were also present. Laboratory examinations revealed low dextrose tolerance, with no change in the sugar content of the blood after injection of epinephrine. Many other investigations were done. On the sixteenth day in the hospital the patient died. Biopsy of the liver revealed low glycogen content. The carbon dioxide–combining power was 34 and 30 volumes per cent; the urea measured 25.6 mg., the calcium 11 mg. and the phosphorus 3.4 mg. per hundred cubic centimeters. Roentgenograms of the long bones revealed marked evidence of rickets. Autopsy revealed that the liver was enlarged and yellow greenish with multiple nodes of various sizes, and microscopic examination revealed annular cirrhosis of atrophic hypertrophic type with severe fatty degeneration. The spleen was congested and enlarged, and the kidneys were hypertrophied, with congestion of interstitial vessels and degenerative lesions of tubules.

Comprehensive discussion of the subject is given, with comments on the etiologic factors and the reported cases.

The de Toni–Fanconi syndrome, according to the authors, is the result of a disturbance of the liver and kidneys selectively affecting certain functions. It is their opinion that it may depend on constitutional, infectious or dietetic factors, or on all three combined.

KEITH, Rochester, Minn.

Nervous Diseases

ABSCESS WITHIN THE SPINAL CORD: REVIEW OF THE LITERATURE AND REPORT OF THREE CASES. PHILIP K. ARZT, Arch. Neurol. & Psychiat. **51**:533 (June) 1944.

Abscess occurs in the spinal cord; it may be single or multiple, occur at any level and be inside or outside the cord itself or the covering membranes. It may be primary, secondary or of unknown origin. The abscess may occur at any age. The signs and symptoms vary with the location and amount of destruction. The prognosis is poor. In the case of a single lesion drainage may be beneficial. Fortunately, these abscesses are rare.

BEVERLY, Oak Park, Ill.

VASOPARALYSIS OF THE CENTRAL NERVOUS SYSTEM, A CHARACTERISTIC VASCULAR SYNDROME: SIGNIFICANCE IN THE PATHOLOGY OF THE CENTRAL NERVOUS SYSTEM. I. MARK SCHEINKER, Arch. Neurol. & Psychiat. **52**:43 (July) 1944.

Pathologic studies indicate that vascular disturbance commonly produces the cerebral edema and tissue changes in cases of cerebral injury. The author feels

that there is a vasoparalysis of the central nervous system, or a "central vasoparalysis." In the cases studied and described in the article vascular disturbances caused by injury to the brain were demonstrated.

BEVERLY, Oak Park, Ill.

SKULL DEFECT AND HERNIATION OF CEREBRUM WITH ABSENCE OF DURA FOLLOWING HEAD INJURY IN ADOLESCENCE. WILLIAM S. MCCUNE and BARNES WOODHALL, Arch. Neurol. & Psychiat. **53**:307 (April) 1945.

The authors describe a case in which degenerative changes in the skull, with destruction of the inner table, absence of the dura over that area and herniation of the brain into the defect occurred in a 32 year old woman. This condition developed seventeen years after a head injury, and a causal relationship is suggested. Other cases of this kind have been described.

BEVERLY, Oak Park, Ill.

CEREBRAL INJURY BY BLUNT MECHANICAL TRAUMA: EFFECTS OF REPEATED IMPACTS OF MINIMAL INTENSITY, WITH OBSERVATION ON EXPERIMENTAL ANIMALS. C. G. TEDESCHI, Arch. Neurol. & Psychiat. **53**:333 (May) 1945.

The author found that repeated subconcussive blows on the heads of rats caused, after a sufficient number had been inflicted, unconsciousness, and possibly death. Pathologically, there were no hemorrhages, but neuronal changes were observed similar to those found after more severe trauma from single blows. The amount of damage was proportional to the number and the strength of the blows.

BEVERLY, Oak Park, Ill.

THE TREATMENT OF PNEUMOCOCCIC MENINGITIS WITH PENICILLIN. LEWIS SWEET, EDITH DUMOFF-STANLEY, HARRY DOWLING and MARK LEPPER, J. A. M. A. **127**:263 (Feb. 3) 1945.

An analysis of the cases of 16 patients is given. Two are in the pediatric age group. The first child, aged 1½ years, had a head injury with complicating pneumonia, bacteremia and meningitis. In the second child, aged 2 months, the meningitis was primary. The 2 children received large doses of penicillin intramuscularly and intrathecally, chiefly into the lateral ventricles, for forty-six and forty-eight days respectively. Both were given antipneumococcic serum. Because of immediate exacerbations of the meningitis following attempts to stop penicillin therapy, sulfadiazine was given in addition to penicillin for another forty-one and sixty days respectively. Both children recovered but had mental deterioration.

BAIRD, Wauwatosa, Wis.

TREATMENT OF TYPE B HEMOPHILUS INFLUENZAE MENINGITIS. HATTIE E. ALEXANDER, J. Pediat. **25**:517 (Dec.) 1944.

Early diagnosis and prompt institution of adequate therapy are of signal importance in the outcome of influenzal meningitis, and the expectation of recovery has been shown in previous papers to correlate closely with these factors. At the same time it must be recognized that a few patients recover even after the lapse of a long delay between the onset of infection and the application of adequate therapy; indeed, some of the patients have experienced complete recovery in spite of the fact that their meningitis had entered what seemed to be a chronic stage. Recovery is attained also by a few of those whose disease appears to include a definitely encephalitic component. An analysis of some of these unusual cases is attempted in the present paper.

When patients are treated early with the combined therapy of sulfadiazine and type-specific rabbit antibody according to the principles outlined, the response has been so consistent that it is possible to predict not only the outcome but the course of recovery. Even when the meningitis progresses so rapidly that the spinal fluid sugar falls to less than 15 mg. per hundred cubic centimeters within twenty-four hours of onset, recovery can be expected to be prompt if sufficient antibody is administered in the initial dose. A favorable course of this kind can be predicted for all patients treated early in the disease, with the exception of one small group. An occasional patient exhibits characteristics of a fulminating infection, which is followed by coma within a few hours after the onset of meningitis. Such patients have proved particularly resistant to all forms of treatment—presumably because a significant degree of encephalitis accompanies the meningitis. An example of this form of the disease, in which a favorable outcome was recently obtained, is presented.

Nowadays virtually all of the failures are due to late treatment or to long-standing inadequate treatment. These include the cases of young infants under 7 months of age for whom diagnosis was delayed because of failure of these patients to exhibit easily recognizable signs of meningeal irritation. In older children irreversible injury of the brain may still be encountered for one or both of two reasons—failure to identify the causative organism and too much confidence in the value of sulfonamide compounds when used without the addition of serum.

Thus, one must expect that failures will continue to be encountered, but experience during the last two years has encouraged the discarding of a defeatist attitude and the persistence in energetic treatment of these patients even when ominous signs are at hand. Five unusual cases are presented in detail.

It must be emphasized that the treatment of the chronic form of Hemophilus influenzae meningitis is still in the experimental stage. The term "chronic" has been used to designate the clinical status of the patient rather than the duration of the disease. In this group are classified all those who have exhibited striking rigidity of the extremities as well as the trunk and who show a preference for the opisthotonic position. While this would be considered the minimal requirement for inclusion in this category, these patients presented additional signs: tremors of extremities and signs caused by damage to cerebral cells.

Two new procedures have been introduced for treatment in the chronic cases: the intrathecal administration of heparin and the introduction of air into the subarachnoid space after removal of appropriate quantities of spinal fluid. The former was used in an effort to prevent the formation of additional fibrinous exudate, and the latter, in an attempt to establish communication beween the presumably walled-off areas of the subarachnoid space by mechanically breaking up adhesions.

It is the intent, when these patients are seen only after the chronic stage is reached, to use heparin intrathecally as part of the initial treatment and to delay intrathecal administration of serum for several days or until it becomes clear that serum given intravenously is not influencing the meningitis. Injection of air in-

trathecally will be reserved for patients who fail to respond to serum and heparin administered intrathecally.

AUTHOR'S ABSTRACT.

PENICILLIN THERAPY IN PNEUMOCOCCIC MENINGITIS. KATHARINE H. BAIRD, J. Pediat. **26**:287 (March) 1945.

A report is given of the case of a 16 month old boy with pneumococcic meningitis and septicemia. After an initial favorable response to sulfadiazine, penicillin administered intramuscularly and intravenously and one dose of penicillin administered intraspinally, the child relapsed. He was then given five doses of penicillin intraspinally, a total of 100,000 units. There was an apparent cure as indicated by the steady fall in cell count of the spinal fluid and by four sterile cultures of spinal fluid. Sixty hours after the last intraspinal injection the child again had a relapse. Penicillin was given intracisternally on two successive days. Because of the persistence of fever and vomiting and a falling spinal fluid sugar level, a block at the base of the brain was suspected. A craniotomy was done, with the introduction of a catheter into the left lateral ventricle. Penicillin was given through the catheter for twelve days, a total of 170,000 units, without ill effect. The child made an apparently complete recovery.

BAIRD, Wauwatosa, Wis.

TREATMENT OF MENINGITIS WITH PENICILLIN INJECTED INTRAVENOUSLY AND INTRAMUSCULARLY. ALLISON HOWE PRICE and JOHN H. HODGES, New York State J. Med. **44**:2012 (Sept. 15) 1944.

Working in the Jefferson Medical College and Hospital, Philadelphia, Price and Hodges were provided with penicillin through the National Research Council. Seven patients suffering from meningitis of various types were treated with this drug, 5 of whom recovered. Two died. One of these had complicating diabetes; the other, hyperthyroidism. Price and Hodges state that the trend of opinion in regard to spinal puncture is that it should be used to determine the diagnosis or the effect of therapy or to relieve intracranial pressure. They are convinced that the intravenous and intramuscular methods of administering penicillin are just as effective as the intraspinal (they used the word "intrathecal"). They described in detail the daily course of their patients. Penicillin was given by the intravenous drip method to the amount of 100,000 units in every twenty-four hours for five days or longer (in case 1, for two weeks). This dosage was then continued intramuscularly until the patients were symptom free. The organisms were pneumococci, staphylococci and meningococci. In summary the authors say: "Two patients with acute meningitis complicated by other systemic disease died a few hours after penicillin was begun. Five patients with coccic meningitis were successfully treated with penicillin injected intravenously or intramuscularly without intrathecal therapy." In an addendum they state that after the report went to press 2 more patients with meningococcic meningitis were thus successfully treated. The case reports are well done and should be read in their entirety.

VOORHEES, New York. [ARCH. OTOLARYNG.]

THE SUDDEN DEATH OF MICE INJECTED INTRAORBITALLY WITH MINUTE QUANTITIES OF SESAME OIL. FRANK H. J. FIGGE, Proc. Soc. Exper. Biol. & Med. **57**:24 (Oct.) 1944.

Numerous experiments were carried out on mice, in which it was observed that the injection of as little as 0.025 cc. of sesame oil or any viscous oil intraorbitally into or near the harderian gland resulted in rapid death within one or two minutes. Immediate autopsies revealed fibrillation of the atria with the ventricles in diastole. Simultaneous administration of atropine sulfate with the oil prevented death, and the author concludes that the oculocardiac reflex was responsible for the sudden death of these mice.

HANSEN, Galveston, Texas.

THE EXCRETION OF PENICILLIN IN THE SPINAL FLUID IN MENINGITIS. DAVID H. ROSENBERG and J. C. SYLVESTER, Science **100**:132 (Aug. 11) 1944.

Rosenberg and Sylvester administered penicillin in doses of 20,000 to 40,000 Oxford units intravenously and intramuscularly to 8 patients with meningitis. For 6 of these patients the condition had been proved to be meningococcic meningitis. Sixty to one hundred and forty minutes after administration penicillin was recovered from the cerebrospinal fluid, following lumbar puncture, in concentrations of 0.03 to 0.35 unit per cubic centimeter.

These data suggest that penicillin administered intravenously or intramuscularly in adequate doses may be effective in the treatment of meningitis without supplementary intrathecal therapy.

GUTTMAN, Philadelphia.
[ARCH. NEUROL. & PSYCHIAT.]

TORULA INFECTION OF THE CENTRAL NERVOUS SYSTEM. C. T. CHAMPION DE CRESPIGNY, M. J. Australia **2**:605 (Dec. 9) 1944.

The author reviews the history of torulosis and reports 2 cases of the disease occurring in adult livestock workers. The 2 patients showed striking differences. The first man was ill for several months with steadily ingravescent symptoms. The pathologic examination showed that the deposits of yeast cells caused but little reaction in the surrounding tissues. Furthermore, the yeasts failed to reproduce the disease in the animals inoculated.

The illness of the second patient was of considerably shorter duration and was divided into two distinct phases. The final meningitic stage was rapidly fatal. At its height, Cryptococci were cultivated from the blood. The tissues showed active local defensive reaction with proliferation of the reticuloendothelium and giant cell formation, in parts resembling tuberculosis and in the lymph glands not unlike lymphadenoma. All the inoculated animals died. Their organs showed much subacute inflammatory reaction. Unfortunately, in the second case the cultural and other characteristics of the tortulas were not studied, but from the very different reactions in the tissues of the hosts it seems likely that the infective agents were of different species or varieties.

GONCE, Madison, Wis.

CONSIDERATIONS CONCERNING A CASE OF PURULENT MENINGITIS DUE TO A HITHERTO UNRECOGNIZED ORGANISM. L. VELASCO BLANCO, H. S. VACCAREZA and C. RECHNIEWSKI, Arch. am. de med. **20**:7 (March) 1944.

A case of purulent meningitis in a 2½ year old girl is presented, in which a peculiar gram-negative anae-

robic bacillus was isolated from the spinal fluid. The spinal fluid showed a cell count of 5,280 cells per cubic centimeter, of which 97.5 per cent were polymorphonuclear leukocytes; the level of the spinal fluid glucose was practically zero. The patient died in spite of intensive treatment with sulfonamide compounds by mouth and intrathecally.

The organism encountered corresponds in morphologic staining, cultural and biologic characteristics to the species of the necrosis bacillus of Schmorl. It differs from it in its lack of pathogenicity for the usual experimental animals.

ABALLI, Habana, Cuba.

FAMILIAL SPASMODIC PARAPLEGIA: REPORT OF THREE CASES. E. CIENFUEGOS and J. N. DANERI, Arch. argent. de pediat. **22**:289 (Oct.) 1944.

Familial spastic paraplegia occurring in 3 boys of a family of six siblings is reported. Pyramidal signs, paraplegia, atrophy of the optic nerve and mental deficiency were present. No sensory disturbances or cerebellar signs were observed, and the onset in all 3 cases occurred at the age of 8 to 12 months.

The authors, after exhaustive differential diagnostic considerations, believe these cases to be atypical instances of familial spastic paraplegia. The early onset, speech disturbances and mental deficiency observed in these cases are not described as characteristic of this disease.

CASSORLA, Chicago.

PURULENT MENINGITIS IN THE INFANT. F. DE ELIZALDE, O. R. TURRO and J. GIUSSANI, Arch. argent. de pediat. **22**:475 (Dec.) 1944.

During the last six years 18 infants with purulent meningitis were treated with sulfonamide compounds. The dosages varied from 0.15 to 1.30 Gm. per kilogram of body weight, the route of administration being oral, intramuscular or intrathecal. The organisms found were Pfeiffer bacilli in 9 infants, pneumococci in 5 and streptococci in 2. No organism was found in the remaining 2 infants. The sulfonamide compounds used were sulfapyridine, sulfathiazole, sulfacetimide and sulfadiazine. Regardless of the dosage or the route of administration, all the drugs failed in 16 instances. The mortality rate was 88.88 per cent; only 2 patients, 1 of them having aseptic meningitis and the other meningitis due to Pfeiffer's bacillus, recovered. Sulfonamide compounds used early during the primary infection were unable to prevent the meningeal complication in 9 children. In all cases complete general care was given, including repeated blood transfusions.

The drug level of the spinal fluid was not consistent with the dosage of sulfonamide compounds administered.

CASSORLA, Chicago.

PROPAGATION OF EPILEPTIFORM IMPULSES IN THE BRAIN: I. ROLE OF THE CORPUS CALLOSUM. SIXTO OBRADOR ALCALDE, Bol. d. lab. de estud. med. y biol., Mexico **1**:29 (April) 1942.

Obrador Alcalde stimulated the cerebral cortex of cats with an alternating electrical current for periods of ten seconds at intervals of two minutes. The corpus callosum was sectioned in 11 animals. There was no significant change in the nature of the induced convulsive seizures after section. In only 1 animal were the convulsions less intense in the limbs ipsilateral to the side of the brain which was stimulated. In a few other animals there was some variation in the convulsive threshold, with slight decrease in intensity of the convulsions. There was no significant variation in the pattern of the attacks. The corpus callosum therefore does not appear to be essential in transmission of epileptigenous impulses from one side of the brain to the other.

SAVITSKY, New York. [Arch. Neurol. & Psychiat.]

Psychology and Psychiatry

PSYCHIC DEAFNESS IN CHILDREN. EMIL FROESCHELS, Arch. Neurol. & Psychiat. **51**:544 (June) 1944.

The author tests deafness with a modified accordion of Victor Urbantschitsch by means of which the tones of forty-two whistles, forming a scale of six octaves ranging from G-1 to f-4 are introduced into the auditory canal by means of rubber tubes and the ability to hear can be determined by reflex changes without the cooperation of the patient. The author found 12 cases of psychically deaf children in examining 60,000 children, and he describes 3 of the cases in this article.

The evidence presented is conclusive that there are children who have functional deafness and who can be successfully treated.

BEVERLY, Oak Park, Ill.

ELECTROENCEPHALOGRAPHIC EVALUATION OF PRIMARY BEHAVIOR DISORDERS IN CHILDREN. JACQUES S. GOTTLIEB, JOHN R. KNOTT and M. COULSON ASHBY, Arch. Neurol. & Psychiat. **53**:138 (Feb.) 1945.

The authors confirmed observations of other writers that the electroencephalographic tracings of children with primary behavior problems are abnormal in about 50 per cent of cases.

BEVERLY, Oak Park, Ill.

THE ENDOCRINE GLANDS IN INFANTILE AMAUROTIC FAMILY IDIOCY. OTTO MARBURG, J. Nerv. & Ment. Dis. **100**:450 (Nov.) 1944.

The characteristic asthenic posture observed in amaurotic familial idiocy may be explained on the basis of degeneration of the chromaffin tissue of the adrenal medulla. In addition, there are a prematurity of the gonads, degeneration of the interstitial cells, a relative hyperplasia of the thymus and an increase of colloid in the thyroid.

The author submits 3 case reports with postmortem anatomic descriptions of the lesions in the endocrine glands. All 3 children presented classic symptoms of Tay-Sachs disease, and all 3 died of pneumonia prior to reaching the cachectic stage.

JAHR, Omaha.

Diseases of the Genitourinary Tract

DEVELOPMENT OF HYPERTENSION ASSOCIATED WITH LESIONS OF THE KIDNEY. HERMAN O. MOSENTHAL, Am. J. M. Sc. **208**:210 (Aug.) 1944.

The author describes a case of hypertension associated with renal lesions that gives the complete picture and furnishes satisfactory evidence in regard to the validity of his statement. He gives the following conclusions:

"Unilateral renal disease may exist for many years without affecting the blood pressure. As compensatory processes for the maintenance of normal arterial tension become strained, periods of intermittent rise in blood pressure occur. Finally, a permanent hypertension may develop. The extirpation of a unilaterally diseased kidney should prevent a rise in blood pressure or remedy

it if it has become permanently established, provided there are no causes for hypertension either in the remaining kidney or elsewhere in the body."

HENSKE, Omaha.

AN APPLICATION OF STAGING IN THE REMOVAL OF DIFFICULT WILMS' TUMOR. EVERETT D. SUGARBAKER, Ann. Surg. **120**:901 (Dec.) 1944.

Wilms's tumors, mixed tumors of the kidney, sometimes called renal embryoma, may occur from fetal life to late adult life but are found most frequently in infancy and early childhood. They grow rapidly to bulky size, metastasize particularly to the liver and lungs, and have a quickly fatal termination.

The usually pronouced regression in the size of the tumor after treatment by external irradiation has led to widespread use of this therapy. However, the author feels that preoperative roentgenotherapy does considerable harm by delaying nephrectomy. He feels that operation alone offers better results. A two stage procedure to minimize bleeding is discussed. Gerota's fascia is described in detail, and its importance in preventing local recurrence is emphasized.

One case, that of a 12 year old boy, is reported.

BANTIN, Omaha.

CARCINOMA OF THE VAGINAL WALL IN A GIRL OF FOURTEEN; RADIATION THERAPY. R. S. SIDDALL, Harper Hosp. Bull. **2**:54 (Dec.) 1944.

Periods of vaginal bleeding occurring rather regularly in a girl of 14 years were thought to be normal menstruation until the bleeding became practically continuous. Eighteen months after the onset, the child was examined and found to have a soft, irregular mass in the region of the cervix. Biopsy showed advanced medullary squamous cell carcinoma. Most of the growth, which was found at operation to be in the anterior lateral vaginal wall and not encroaching on the cervix, was removed by curetting and 100 mg. of radium was implanted. Details of the series of radium treatments are given. Since these treatments, there has been no recurrence of the tumor over a period of two years and five months. A normal growth of pubic hair and other secondary sexual characteristics have appeared, but there has been nothing suggesting menstruation since early in the treatment.

LESLIE, Evanston, Ill.

INTESTINAL HERNIA WITH EVERSION AND EXSTROPHIC BLADDER. JOHN G. SINCLAIR, J. Pediat. **26**:78 (Jan.) 1945.

An infant lived 2½ months with an extensive congenital and probably gene-determined developmental anomaly. The ileum and colon were completely separated. The yolk stalk and urogenital sinus remained open on the body surface. The ileum was herniated and everted 3 inches (7.6 cm.) through the umbilical cord, and the colon was everted over a smaller area. The epithelium of the bladder was external, the ureters opening to the surface. Defects of form and number of the lumbar and sacral vertebrae were associated with nearly normal sacrum and limbs. Female internal genitals included a double uterus. Other parts were normal. The liquid intake was good, yet the infant died dehydrated from losses through the externalized mucosa.

SINCLAIR, Galveston, Texas.

A CASE OF PENTOSURIA WITH DIABETIC SYMPTOMS. M. G. PETERMAN, J. Pediat. **26**:296 (March) 1945.

A case of pentosuria in a Jewish male infant is reported, in which all the symptoms of diabetes were present. There was also a family history of diabetes on both sides. The sugar in the urine proved to be a pentose, and the sugar tolerance was normal on several occasions. Some symptoms persisted for two years, after which the urine cleared.

AUTHOR'S ABSTRACT.

SOME PROBLEMS OF PEDIATRIC GYNECOLOGY. B. BERNARD WEINSTEIN, New Orleans M. & S. J. **97**:495 (May) 1945.

The author stresses the well known fact that pediatricians have never given the female genital tract the attention it rightly deserves. The treatment of gonococcic vaginitis is discussed. The uterus, except for rare benign or malignant tumors, is reported as a rare source of difficulty. The tubes may be involved in hematosalpinx and pyosalpinx. Tuberculous salpingitis can occur with tuberculosis in other organs. Pelvic peritonitis may occur and be confused with acute appendicitis, ruptured appendix, Meckel's diverticulitis, mesenteric lymphadenitis and iliac adenitis. Menstrual disorders are discussed in some detail, as are menometrorrhagia and dysmenorrhea.

The article, although not long, is comprehensive and informative. Its reading is recommended to any one wishing a short review of a fascinating and neglected subject.

BERKLEY, Los Angeles.

ANURIA: REPORT OF FOUR CASES: THREE TREATED BY KIDNEY DECAPSULATION. CHARLES MARQUARDT, HAROLD COOK and ANTHONY FREDERICK, Wisconsin M. J. **43**:1218 (Dec.) 1944.

One of the 4 cases reported is that of a 5 year old child in whom anuria developed subsequent to ingestion of mercury bichloride. Forty-nine hours after the onset of anuria decapsulation of the right kidney was done and sixty hours later decapsulation of the left. Urinary secretion increased to normal with corresponding clinical improvement, but the child finally died of perforation of the bowel with peritonitis, two weeks after the ingestion of the poison.

BAIRD, Wauwatosa, Wis.

RENAL DWARFISM: RENAL HYPERPARATHYROIDISM WITH OSTEOPOROSIS. L. VELASCO BLANCO and D. SILBERBERG, Arch. am. de med. **19**:30, 1943.

A case of dwarfism in a 13 year old child who was suffering from a severe chronic glomerulonephritis is described. The urine contained albumin and granular casts. The specific gravity remained between 1.003 and 1.005, and there was a polyuria of 3 liters daily. Roentgenograms of the skull showed no changes in the sella turcica. There was a pronounced osteoporosis in the long bones and a delayed appearance of centers of ossification at the wrist. The urea in the blood reached a level of 222 mg. per hundred cubic centimeters, and that in the spinal fluid increased to 300 mg. near the end.

Renal function tests were not performed, and determinations of blood calcium, phosphorus, carbon dioxide and phosphatase were not made.

The patient died of uremia, but autopsy was not performed.

ABALLI, Habana, Cuba.

Diseases of the Ductless Glands; Endocrinology

NEUROMUSCULAR TRANSMISSION IN PARATHYROID TETANY. F. VALENZUELA, F. G. HUIDOBROTORO and R. VALDES, Proc. Soc. Exper. Biol. & Med. **57**:31 (Oct.) 1944.

The thyroid and parathyroid glands were removed from 31 cats, after which the neuromuscular transmission was studied by high frequency stimulation of the nerve and tracings made by fixation of the soleus muscle. The serum calcium, which was determined for half the animals, was between 4.6 and 7.6 mg. per hundred cubic centimeters (normal, 12 mg.). Thyroid extract was given to 6 cats, and calcium chloride, 0.2 cc. of a 2 per cent solution per kilogram, was given intravenously to 8 other cats. The character of the tracings obtained was distinctly abnormal. Certain stages (referred to as 3 b and 3 c) did not appear. The other various stages disappeared, and the muscles showed a decided tendency to fatigue; administration of thyroid extract did not produce normal tracings, whereas calcium chloride readily did. The authors assert that, inasmuch as the chemical transmitter of neuromuscular synapse is acetylcholine, and, as Harvey and MacIntosh (*J. Physiol.* **97**:408 [Jan.] 1940) have shown, the calcium ion is essential for cholinergic transmission, it is the decrease in calcium ions which hinders the release of acetylcholine, thereby accounting for the pronounced fatigability of the neuromuscular synapse in animals with parathyroid tetany.

HANSEN, Galveston, Texas.

EFFECT OF ETHER EXTRACT OF THE THYMUS AND PANCREAS ON SYNTHESIS OF ACETYLCHOLINE. CLARA TORDA and HAROLD G. WOLFF, Proc. Soc. Exper. Biol. & Med. **57**:69 (Oct.) 1944.

Ether extracts of the thymus and pancreas were found to depress the synthesis of acetylcholine in vitro, whereas similarly obtained extracts of lymph nodes, thyroid, salivary glands, lungs and subcutaneous fat had no such effect. Intravenous injection of extract of thymus and pancreas into cats and rabbits decreased the effectiveness of the serum (specimens taken one-half to twenty-two hours after injection) to inhibit acetylcholine synthesis. The ability to depress this synthesis appeared within one hour but disappeared between ten and twenty-two hours after the injection, and the decrease amounted to as much as 45 per cent. The extracts of the thymus and pancreas contained neither nucleoproteins nor their decomposition products. Patients with myasthenia gravis may benefit from removal or irradiation of the thymus. Previous work of the authors disclosed that less acetylcholine was synthesized in the presence of serum and spinal fluid from patients with myasthenia gravis than from control subjects.

HANSEN, Galveston, Texas.

LIPODYSTROPHY FOLLOWING INSULIN THERAPY. L. EXPOSITO, A. DE FERIA and H. GONZALEZ, Bol. Soc. cubana de pediat. **15**:723 (Nov.) 1943.

The authors present 2 cases of lipodystrophy following repeated injections of insulin in 2 diabetic children, the one case of the atrophic type, in a white girl 3½ years of age, and the other of the tumoral variety in a white girl 13 years of age. They give a review of the literature, including the history, clinical description, etiologic factors and pathologic changes.

Only one type of lesion has been observed in the same patient. The dystrophy tends to disappear when the point of injection is changed, although in the atrophic type the recovery is slower and may never be complete.

KEITH, Rochester, Minn.

Diseases of the Muscles, Bones, Joints and Lymph Glands

ALBRIGHT'S SYNDROME. ALBERT BEHREND, Ann. Surg. **121**:245 (Feb.) 1945.

The author presents in detail a case of Albright's syndrome occurring in a 7 year old girl.

In 1937, Albright and his associates described this syndrome which is characterized by (*a*) osseous lesions which have a decided tendency to be unilateral and which on histologic examination show osteitis fibrosa; (*b*) brown nonelevated pigmented areas of the skin, which tend to be on the same side as the osseous lesions, and (*c*) an endocrine dysfunction which in girls is associated with precocious puberty.

To date, 34 cases have been reported. The causation of the condition is a matter for conjecture. No specific form of therapy is known, and the prognosis is uncertain.

BANTIN, Omaha.

PENICILLIN IN THE TREATMENT OF CHRONIC OSTEOMYELITIS. DONALD G. ANDERSON, LOUIS G. HOWARD and CHARLES H. RAMMELKAMP, Arch. Surg. **49**:245 (Oct.) 1944.

The authors present a preliminary report of a series of 40 cases of chronic osteomyelitis in which treatment with penicillin has been employed. In 25 of these cases it has been possible to conduct follow-up observations for one year or longer after completion of the first course of treatment with penicillin. The total dose of penicillin ranged from 400,000 to 5,500,000 units. The duration of treatment varied from two to fifty-six days. In 12 cases operation was performed concomitantly with the administration of penicillin. A second course of penicillin therapy was given in 9 cases in which there was relapse. The results were on the whole satisfactory. The infection was arrested in 32 cases. There was an improvement in 2 cases, no improvement in 5 and 1 death. This was the situation following the first course of treatment.

KAISER, Rochester, N. Y.

THE CLINICAL DIAGNOSIS, PROGNOSIS AND TREATMENT OF ACUTE HEMATOGENOUS OSTEOMYELITIS. FRANK D. DICKSON, J. A. M. A. **127**:212 (Jan. 27) 1945.

Ninety per cent of the cases of acute hematogenous osteomyelitis are due to staphylococci, but in children under 2 years 40 to 50 per cent are due to streptococci. The bacteremia resulting from an infection of the upper part of the respiratory tract may result in two types of disease. There may be localization in bone. typically in the metaphysis of long bones—a new theory to explain such localization is the involvement of the abundant reticuloendothelial tissue there—or there may be a septicemia with abscesses in bone and elsewhere. The latter is the fulminating type of infection, which is not primarily osteomyelitis and should not be regarded as such.

The clinical picture of the first type is that of sudden onset of an acute illness, with pain in the involved extremity. Early localized tenderness over the involved

area is an important early sign, as is the fact that flexion of the joint may be permitted but extension may be found painful. Culture of blood is important for diagnosis.

The authors believe that for children under 2 years treatment should be conservative, with simple aspiration of pus often the only surgical instance needed. For older patients they believe that adequate early surgical drainage should be done provided the patient can tolerate surgical treatment and the disease is of localized type. The sulfonamide compounds are of great value but too frequently leave an active focus of infection unless combined with operation.

BAIRD, Wauwatosa, Wis.

PRECOCIOUS SKELETAL DEVELOPMENT. ROGER L. J. KENNEDY, J. A. M. A. **127**:580 (March 10) 1945.

Precocious skeletal development is not limited to any single clinical syndrome nor is it always associated with any syndrome, not even adrenal cortex disease with increased urinary excretion of androgens. Twenty-three cases of precocious skeletal development are given. In 3 the condition was associated with tumors of the adrenal cortex, and in 12 adrenal hyperplasia was either proved or suspected. In 3 cases the precocious development may have been induced by endocrine therapy. The remaining 5 were miscellaneous cases without any apparent adrenal disease.

BAIRD, Wauwatosa, Wis.

THE ROENTGENOLOGICAL DIAGNOSIS OF SKELETAL DISEASES OF INFANTS AND CHILDREN. RALPH S. BROMER, Minnesota Med. **27**:895 (Nov.) 1944.

In a good review, the author discusses some of the more noteworthy contributions to the roentgenologic knowledge of skeletal diseases in infants and children. Mention is made of the changes produced by vitamin deficiency diseases, such as rickets, late rickets, renal rickets and infantile scurvy, and those produced by lead poisoning, leukemia, chronic hemolytic anemias, sickle cell anemia, celiac disease, xanthomatosis, Gaucher's disease and congenital syphilis. The paper is well worth reading.

STOESSER, Minneapolis.

ACUTE POLYARTHRITIS IN QUEENSLAND. E. W. SIBREE, M. J. Australia **2**:565 (Nov. 25) 1944.

The author reports on 28 cases of polyarthritis which occurred as a small epidemic in a military unit in Queensland in late February and early March 1944. The course of the disease was usually mild, but a few patients required prolonged treatment. Malaise, if present, was usually the first complaint; it was followed in about two days by a rash and by pain in the joints, which appeared simultaneously, or within a day of each other. Involvement of joints was usually multiple, two or more joints becoming painful at about the same time and remaining painful throughout, without subsequent involvement of other joints. Both small and large joints were involved. Pain and tenderness were not accompanied with redness and swelling. The articular involvement was the last clinical manifestation to disappear. The rash consisted of small discrete pink papules, was generalized in distribution and persisted for three to eight days. Superficial adenitis was present in 11 cases. The decrease was not accompanied with severe constitutional disturbance; apyrexia was the rule, and when fever did occur the temperature did not exceed 101.4 F.

GONCE, Madison, Wis.

OSTEOMYELITIS IN A FORTY-FIVE DAY OLD GIRL. E. G. CASELLI, S. GOROSTIAGUE and R. J. DELLEDONE, Arch. argent. de pediat. **22**:500 (Dec.) 1944.

The authors describe a case of osteomyelitis in a 45 day old girl. Swelling of the left knee and fever were the first signs. A week later, fluctuation was noticed; the roentgenograms showed involvement of the distal epiphysis of the femur. The patient was operated on, and a sulfonamide compound was given, both locally and orally. Recovery took place in fifteen days. The authors review the literature and describe the characteristics of this condition. The following points are stressed: (1) the guarded prognosis during the invasion period, (2) the early appearance of osseous destruction and (3) the importance of the skin and respiratory tract as sites of the primary infection.

CASSORLA, Chicago.

GRISEL'S DISEASE, OR NASOPHARYNGEAL TORTICOLLIS. L. EXPOSITO, A. DE FERIA and H. GONZALES, Bol. Soc. cubana de pediat. **15**:731 (Nov.) 1943.

This disease is characterized by acute torticollis, which produces permanent distorted position.

Of sudden onset, it is always associated with an infectious process of the nasopharynx, followed by changes in the cervical portion of the spine due to rotation of the atlas in relation to the axis.

The history, a review of literature and a complete description of the illness, including the diagnosis and pathogenesis, are given.

There is a summary in English of the clinical case presented.

KEITH, Rochester, Minn.

Diseases of the Eye

ORBITAL CELLULITIS TREATED SUCCESSFULLY WITH PENICILLIN. H. O. SLOANE, J. A. M. A. **126**:164 (Sept. 16) 1944.

The author supplies the following summary:

"In a case of orbital cellulitis of the left eye in a boy of 12 the cause was established to be sinusitis involving the left ethmoids and the maxillary antrum. Operation was contemplated both for the sinus condition and locally to establish drainage and relieve the inflammation and swelling of the orbital tissues. However, under the continued use of penicillin intravenously for a period of ten days the condition cleared up completely, so that it was unnecessary to operate. Sulfadiazine in fairly large doses was tried without affecting the disease in any way and was discontinued when penicillin was administered. Local treatment was limited to applications of hot magnesium sulfate solution continuously and instillation of atropine sulfate 1 per cent three times daily."

ZENTMAYER. [ARCH. OPHTH.]

ORBITAL CELLULITIS WITH SEVERE CEREBRAL SYMPTOMS. JEROME ROMAGOSA and G. D. RACKLEY, New Orleans M. & S. J. **97**:276 (Dec.) 1944.

The cure of what seemed to be a possible cavernous sinus thrombosis following therapy with sulfamerazine and penicillin is reported. Two cultures of blood taken during the course of the disease were sterile.

BERKLEY, Beverly Hills, Calif.

CONGENITAL PARALYSIS OF BOTH EXTERNAL RECTI TREATED BY TRANSPLANTATION OF EYE MUSCLES. J. A. MAGNUS, Brit. J. Ophth. **28**:241 (April) 1944.

Magnus operated on a patient with bilateral abducens paralysis and pronounced right hyperphoria due to an overacting right inferior oblique muscle. The O'Connor technic of transplantation was used. The cosmetic effect was satisfactory, but abduction was practically impossible. An unusual finding was abnormal thickness of the external rectus muscle, with an abnormal anatomic position of the left eye.

ZENTMAYER. [ARCH. OPHTH.]

CONGENITAL ECTROPION ASSOCIATED WITH BILATERAL PTOSIS: CASE REPORT. S. GORDON, Brit. J. Ophth. **28**:520 (Oct.) 1944.

Gordon reports a case of congenital ectropion of all four lids, with associated ptosis of the upper lids. The facial bones were normal. A satisfactory correction of the defects was obtained by inserting into each upper lid a thin Thiersch graft cut from the arm and into the lower lids a Wolfe graft of postauricular skin. Four months later facial slings attaching the upper lids to the frontalis muscle overcame the ptosis.

The article is illustrated.

ZENTMAYER. [ARCH. OPHTH.]

ANGIOMA OF THE RETINA. I. C. MICHAELSON, Brit. J. Ophth. **28**:522 (Oct.) 1944.

A sergeant complained of sudden onset of defective vision in the left eye two weeks previously. Visual acuity with a correction of -6.50 D. sph. $\bigcirc$ -0.50 D. cyl., axis 180 was 6/36. Examination of the fundus showed a large retinal detachment, chiefly in the lower quadrant, with a tear in the 4 o'clock meridian about 12 mm. from the disk. The inferior temporal artery and vein were broad and tortuous and appeared to end in a raspberry-colored angioma, of about ⅓ disk diameter. General medical examination revealed nothing abnormal.

Micropuncture was made into the tumor, and three micropunctures were made in a vertical line up and in from the tumor with the intention of catching the feeding artery. Surface diathermy with the micropuncture was used. About three months later visual acuity was 6/9, and the visual field had increased in size. The retina was in position; the tumor appeared occluded; the feeding artery was of normal size, and the draining vein could not be definitely traced.

The article is illustrated.

ZENTMAYER. [ARCH. OPHTH.]

Skin Diseases; Allergy

PERLÈCHE—ITS NOSOLOGIC STATUS. CLARK W. FINNERUD, J. A. M. A. **126**:737 (Nov. 18) 1944.

Perlèche should be regarded no longer as a disease entity but rather as an abnormal cutaneous change occurring in the form of an intertrigo of the labial commissures. Probably, therefore, this term should be appropriately modified in use in order to suggest in a specific instance the cause or the nature of the condition which it names: Infectious perlèche could apply to the condition when it is considered to be primarily of bacterial or mycotic origin. Malocclusion, or mechanical perlèche, might signify the condition (as seen in elderly persons) when it is caused by a mechanical agent, such as ill fitting dentures. Vitamin deficiency perlèche could specify the condition when it is of hypovitaminotic or avitaminotic origin. Idiopathic perlèche could designate the condition in instances in which no causative factors can be determined.

HENSCHEL, Denver. [ARCH. DERMAT. & SYPH.]

THE RELATIONSHIP BETWEEN SPONTANEOUS ALLERGIC CONDITIONS AND ASCORBIC ACID: AN EXPERIMENT EMPLOYING SKIN TESTS AND ASCORBIC ACID ON SUBJECTS WITH HAY FEVER. HERBERT LEON NEWBOLD, J. Allergy **15**:385 (Nov.) 1944.

The author conducted an experiment on 8 young men who had had hay fever since childhood. He injected ragweed extract and then administered ascorbic acid orally.

All the men were cutaneously sensitive to short ragweed. None of the tests were done during an active period of hay fever. The ascorbic acid was given orally. The amount varied from 1,000 mg. on the first day and 500 mg. on the second and third day to 1,000 mg. a day for six days. None of the vitamin was given on the day of the test. A breakfast low in ascorbic acid was given on the day of the second test.

The author concludes that ascorbic acid used in this way has no effect on cutaneous reactions due to injection of ragweed extract. He realized that this does not prove that ascorbic acid can have no clinical values.

HOYER, Cincinnati.

URTICARIA CAUSED BY CHLORINATED DRINKING WATER. M. J. GUTMANN, J. Allergy **15**:395 (Nov.) 1944.

Gutmann reports 2 cases of giant urticaria caused by chlorinated drinking water.

HOYER, Cincinnati.

ENDOCRINE ALLERGY: 1. ALLERGIC SENSITIVITY TO ENDOGENOUS HORMONES. BERNARD ZONDEK and Y. M. BROMBERG, J. Allergy **16**:1 (Jan.) 1945.

This is a long and interesting article but difficult to abstract.

In the last paragraph of their summary the authors state the problem briefly: "The results of our investigation lead us to assume that certain gynecologic conditions like pruritus vulvae, and various premenstrual disorders are conditioned by allergy to endogenous hormones. This is also true for disturbance known to be of allergic nature (asthma, vasomotor rhinitis, angioneurotic edema, and urticaria) related to menstruation or menopause."

HOYER, Cincinnati.

BLOOD STUDIES IN ALLERGY: 3. CELLULAR REACTIONS IN SULFONAMIDE SENSITIVITY. THERON G. RANDOLPH and FRANK F. A. RAWLING, J. Allergy **16**:17 (Jan.) 1945.

A comprehensive study of the blood cells of 3 patients following the ingestion of a sulfonamide compound to which they were known to be sensitive was made by the authors.

Ingestion of the drug produced an initial diminution of leukocytes and eosinophils, which was followed by an increase in leukocytes, due in part to young myeloid cells.

The eosinophils returned to the preingestion count or above it when the constitutional symptoms subsided.

The authors feel that "the clinical and hematological response in these cases supports the thesis that an

allergic mechanism is responsible for the described reactions."

HOYER, Cincinnati.

EVALUATION OF THE HISTAMINE INTRADERMAL TEST AS A GENERAL INDICATOR OF ALLERGY. LAURENCE FARMER, J. Allergy **16**:44 (Jan.) 1945.

In regard to the value of the histamine intradermal test as an indicator of allergy the author concludes: "It is not possible to differentiate allergic individuals from nonallergic ones by the use of intradermal histamine test."

HOYER, Cincinnati.

DERMATITIS FOLLOWING THE LOCAL APPLICATION OF SULPHANILAMIDE. B. FISHER, M. J. Australia **2**:449 (Oct. 28) 1944.

Twelve patients considered as having been sensitized to sulfanilamide by the application of the drug to the skin were given scratch tests in order to prove their sensitivity. Sulfanilamide powder was dusted over the scratches, and the area was sealed off with cellophane and adhesive plaster. Two patients showed local and general reactions in twelve hours. The other 10 patients showed local reactions after twenty-four hours. The powder was then removed, but in 4 of the 10 patients a generalized papular rash developed in the next twenty-four hours on the previously affected areas. The ingestion of 0.5 Gm. of sulfanilamide by 8 of these patients after the disappearance of all symptoms elicited by the scratch tests excited the reappearance of the cutaneous manifestation in all 8. The author recommends that the local application of sulfanilamide be limited to the treatment of cutaneous conditions for which the indication is certain, that the treated area be inspected every day for signs of adverse reactions and that the treatment be discontinued immediately on the appearance of a local or general reaction.

GONCE, Madison, Wis.

PITYRIASIS LICHENOIDES CHRONICA (PARAPSORIASIS GUTTATA). A. BURROWS, Proc. Roy. Soc. Med. **38**:126 (Jan.) 1945.

The case of a boy 8 years of age is reported. He had suffered from a nonirritating, slowly spreading rash on the trunk, buttocks and proximal parts of the extremities for five years. The eruption was completely unresponsive to treatment, including ultraviolet irradiation.

WILLIAMSON, New Orleans.

Surgery and Orthopedics

EFFECT OF TOPICAL APPLICATION OF VITAMINS AND SOME OTHER CHEMICALS ON THE HEALING OF WOUNDS. GROSVENOR W. BISSELL, Arch. Surg. **49**:225 (Oct.) 1944.

Recognizing the general growth-promoting properties of the vitamins, the authors studied the effects of various substances when applied directly to wounds. Topical applications were made on wounds of uniform size in normal rats. The substances studied were vitamins A, C, D and E, thiamine hydrochloride, nicotinic acid, riboflavin and other preparations. No definite benefit was derived from the use of any of these substances.

KAISER, Rochester, N. Y.

Teeth and Dentistry

A PHYSICIAN LOOKS AT SCHOOL DENTAL PROGRAMS. GEORGE M. WHEATLEY, Am. J. Pub. Health **33**:12(
(Feb.) 1943.

The author reviews experiences with the development of an economical school dental program among 6,410 children in eight schools for the 1937-1938 school year (Astoria School Health Study). The school principals sent a letter to the parents of each child advising that the child have a dental examination. The private dentists serving this area agreed to give a dental examination to any child coming to their offices accompanied by a parent. In all, 5,681 pupils (88 per cent of the total) were examined. Twenty-one per cent of the number examined needed no treatment. Parents of 1,859 children (29 per cent of the total) took no action. Twelve per cent did not consult a dentist, and 17 per cent did not obtain the recommended treatment. Private dentists examined two thirds of the school children registered, supplied almost three quarters of the treatment services and were responsible for 82 per cent of the patients' completing treatment. The younger the child, the less successful was this plan. Only 56 per cent of the kindergarten group reached a dentist, whereas at least 90 per cent of the pupils above the fourth grade received dental examinations. Another study is cited which indicates that this record can be improved by means of a personal interview with those parents who do not respond to a written note. This supplementary interview, with a dental hygienist or some school health worker, is probably necessary for the younger age groups.

The author believes that dental examinations of school children should be done in the dentist's office rather than in the school, since 80 to 90 per cent of the children will require treatment, which is usually given in the dentist's office. This plan does not increase the school health budget, utilizes the dentists of the community in the school program, trains the pupils to seek treatment facilities in the community and impresses them with the idea that payment for dental care is worth while.

PLATT, Gouverneur, N. Y. [ANGLE ORTHODONTIST]

STUDIES ON THE INCIDENCE AND CAUSE OF DENTAL DEFECTS IN CHILDREN. MARCU BRUCKER, J. Dent. Research **22**:107 (April) 1943.

In this study of the teeth of 5,103 public school children of ages 5 to 15, it was found that freedom from active caries, either by reason of adequate fillings or through immunity, was associated with frequent brushing of the teeth and clean teeth. Fewer children who seldom or never brushed the teeth were free of caries.

BURRILL, Chicago. [ANGLE ORTHODONTIST]

STUDIES ON THE INCIDENCE AND CAUSE OF DENTAL DEFECTS IN CHILDREN. MARCU BRUCKER, J. Dent. Research **22**:309 (Aug.) 1943.

In a study of 1,634 public school children, it was found that there was more gingivitis among children with dirty mouths than among those with clean mouths. The incidence of dental decay was greater than the incidence of gingivitis, but children with gingivitis tended to have more cavities than children with healthy gingivas. It was concluded, among other things, that the findings indicated no correlation between the incidence of caries and the incidence of gingivitis.

BURRILL, Chicago. [ANGLE ORTHODONTIST]

TUDIES ON THE INCIDENCE AND CAUSE OF DENTAL DEFECTS IN CHILDREN: VI. PITS AND FISSURES. MARCU BRUCKER, J. Dent. Research **23**:89, 1944.

TUDIES ON THE INCIDENCE AND CAUSE OF DENTAL DEFECTS IN CHILDREN: VII. FISSURES AND CARIES, ibid. **23**:101, 1944.

From clinical studies, field observations and statistical udies on the incidence of caries in the first permanent olars of large groups of white and Negro children, e author was unable to find any direct relation be- ween the presence of defective fissures and caries.

SANFORD, Chicago. [ANGLE ORTHODONTIST]

N INDEX OF THE PREVALENCE OF DENTAL CARIES IN SCHOOL CHILDREN. JOHN W. KNUTSON, Pub. Health Rep. **59**:253, 1944.

The data utilized for this study were collected by the nited States Public Health Service from studies on e age-specific prevalence of dental caries in school hildren of several communities. "The relationship etween the percentage of children of a specific age ith one or more carious permanent teeth (y) and the verage number of carious permanent teeth per child (x) of that age can be satisfactorily described by the quation $97 - y = 97\ (0.524)^x$. The application of e equation to the problem of collecting prevalence ata on dental caries is discussed. In particular it is own that satisfactory estimates of the average number carious (DMF) permanent teeth per child in a com- unity may be obtained by determining the proportion children by single years of age who have one or ore DMF permanent teeth."

LEWIS, Dayton, Ohio. [ANGLE ORTHODONTIST]

A CASE OF OSTEOMYELITIS OF THE ODONTOID PROCESS OF THE AXIS. F. ARDEN and E. H. DERRICK, M. J. Australia **2**:487 (Nov. 4) 1944.

The authors report the case of a child, aged 1 year nd 10 months, in which the pathogenesis was as fol- ows: tonsillitis, purulent cervical adenitis, bacteremia nd metastatic foci in the right lung and in the axis. pneumothorax followed the pulmonary lesion. The steomyelitis of the axis led to a retropharyngeal abscess s well as to damage to the odontoid process and a eneral looseness of the neighboring ligaments. Hyper- nsion of the head at the time of opening of the retro- haryngeal abscess caused separation of the epiphysis of e odontoid, dislocation of the atlas, compression of e cord and sudden death. The infecting organism as Staphylococcus aureus.

GONCE, Madison, Wis.

URNS IN CHILDREN—A SOCIAL PROBLEM. GILBERTO MOREY S., Rev. Hosp. d. Niño **6**:167 (June) 1944.

Among 293 patients with burns admitted to the hildren's Hospital (Lima, Peru) in the four years and x months from 1940 to June 1944, 44 deaths occurred children under 9 months of age. The most common use was burning of the bedclothes. In the age group 9 months to 4 years, the commonest cause of burns as hot liquids, milk and soup. In this group were 1 patients, with 32 deaths. In the 5 to 8 year old roup, of 77 children, burns were due to various sub- ances within reach of the investigating child, such as lluloid, gunpowder and gasoline. There were 6 aths from such burns. In the 9 to 12 year old group, 44 children, burns were due to any and every known cause—in the main to "domestic activities." There were 2 deaths in this group.

Recommendations are outlined for treatment and prophylaxis.

KEITH, Rochester, Minn.

Miscellaneous

SARCOIDOSIS OF BOECK: METABOLIC STUDIES OF 3 CASES. B. M. STUART, Am. J. M. Sc. **208**:717 (Dec.) 1944.

Stuart gives a brief review of the historical, etiologic, pathologic and clinical aspects of sarcoidosis and presents 3 cases, including 2 with Heerfordt's uveo-parotid syndrome. He also discusses the possibility of sarcoid lesions of the heart in 1 case.

Serum acid phosphatase values in these 3 cases were found to be within normal limits, while serum alkaline phosphatase values were elevated. Other metabolic studies merely confirmed findings previously reported by other investigators. No additional information concerning the cause was revealed by these studies.

HENSKE, Omaha.

THE CONCENTRATION OF PENICILLIN IN VARIOUS BODY FLUIDS DURING PENICILLIN THERAPY. JEAN COOKE and DAVID GOLDRING, J. A. M. A. **127**:80 (Jan. 13) 1945.

This study of concentration of penicillin in body fluids was carried out on 40 patients, mostly children, from the St. Louis Children's Hospital.

The concentration of penicillin in the blood is highest within thirty minutes after subcutaneous or intramuscular injection and falls 50 per cent by the end of the first hour and more rapidly thereafter. Absorption is no slower nor more painful from subcutaneous than from intramuscular injection. Occasional poor clinical responses to therapy are observed in patients with unexplained low blood levels. Higher blood levels may be found in persons with renal insufficiency. There is no close correlation between dose per kilogram of body weight and blood level. Some cumulative effect may be observed. Continued intramuscular or subcutaneous injections at one hour intervals will give a persistent high blood level, and this method may be preferable to intravenous administration for children.

The concentration of penicillin in subcutaneous tissues and serous cavities tends to approximate that in the blood. Large doses injected parathecally give only a low level in the spinal fluid. The persistence of penicillin in the spinal fluid following intrathecal injection depends on the dose injected.

BAIRD, Wauwatosa, Wis.

ADMINISTRATION OF PENICILLIN BY MOUTH: PRELIMINARY REPORT. PAUL GYÖRGY, H. N. VANDEGRIFT, WILLIAM ELIAS, L. G. COLIO, F. M. BARRY and J. D. PILCHER, J. A. M. A. **127**:639 (March 17) 1945.

Administration of penicillin (10 to 40,000 units) by mouth in combination with trisodium citrate (1 to 5 Gm.) was found to be therapeutically effective in 23 cases of gonorrhea and in 3 of other diseases. The effective doses were comparable to those used generally for parenteral administration. The combination, administered orally, gave greater and more prolonged increase of blood levels of penicillin in the 24 patients studied than penicillin ingested alone.

BAIRD, Wauwatosa, Wis.

CHAETOMIN. A NEW ANTIBIOTIC SUBSTANCE PRODUCED BY CHAETOMIUM COCHLIODES: II. ISOLATION AND CONCENTRATION. WALTER B. GEIGER, JEAN E. CONN and SELMAN A. WAKSMAN, J. Bact. **48**:531 (Nov.) 1944.

A certain strain of Chaetomium cochliodes produces an antibiotic substance, designated as chaetomin. It is highly active against gram-positive bacteria but has little effect on gram-negative organisms. The authors made a complete study of the extraction and purification of chaetomin and observed some of the chemical and biologic properties of their highly potent preparation. They found that chaetomin is obtainable both from the culture filtrate and from the mycelium of C. cochliodes. The preparation has been found to be present in much larger quantities in the mycelium than in the culture filtrate. It is extracted from the filtrae by ethyl acetate and from the mycelium by acetone and is repurified by washing with sodium bicarbonate and sodium carbonate. It contains nitrogen and sulfur, but differs greatly in biologic activity from gliotoxin and penicillin.

STOESSER, Minneapolis.

METHODS OF MEASURING PENICILLIN CONCENTRATIONS IN BODY FLUIDS. WILLIAM M. M. KIRBY and LOWELL A. RANTZ, J. Bact. **48**:603 (Nov.) 1944.

Kirby and Rantz state that determinations of penicillin concentrations in body fluids are tedious, time consuming and relatively inaccurate. However, they are of great aid in establishing and evaluating various modes of administration of penicillin, for they indicate whether an effective concentration is present at any given time. Of the three methods developed in connection with the production of penicillin, the Oxford cup technic is the least useful clinically because the concentrations in body fluids are usually too small to produce adequate zones of inhibition. The authors feel that the serial dilution technic is unquestionably the most suitable for routine clinical use. It is relatively simple to perform and sufficiently accurate for most purposes, and the results are clearcut and reproducible. In their modification described in this paper, tube dilutions are substituted for serial dilutions to give greater accuracy in the range of levels which usually occur in blood and urine. As to the turbidimetric method developed in their laboratory, they state that it is highly accurate but impractical for most purposes. Except for highly specialized research procedures, the turbidimetric technic will probably be little employed.

STOESSER, Minneapolis.

MICROBIOLOGICAL ASPECTS OF PENICILLIN: VII. BACTERIAL PENICILLINASE. H. BOYD WOODRUFF and JACKSON W. FOSTER, J. Bact. **49**:7 (Jan.) 1945.

The authors have made extensive studies concerning the destruction of penicillin. They have found that the ability to destroy penicillin is a property widespread among bacteria, yeasts and fungi, aerobic spore-forming bacteria and certain actinomycetes being outstanding in this respect. The substance or enzyme named penicillinase, which is excreted by bacteria and which destroys penicillin, was studied, and its chemical and biologic properties were observed, together with experiments relating to its formation by bacteria. For details concerning the studies made by the authors, the original paper should be consulted.

STOESSER, Minneapolis.

PENICILLIN: III. THE STABILITY OF PENICILLIN IN AQUEOUS SOLUTION. ROBERT G. BENEDICT, WILLIAM H. SCHMIDT, ROBERT D. COGHILL and A. PAUL OLESON, J. Bact. **49**:85 (Jan.) 1945.

In previous experiments with crude penicillin the authors presented data which show that the optimum stability of penicillin in aqueous solution occurred at a p_H between 5.6 and 6.1 instead of 7.0. Furthermore it was expected at that time that crude penicillin would prove to be less stable than the crystalline material. In the present investigations the authors employ a crystalline sodium salt of penicillin. The initial concentration was of sufficient potency that reasonably accurate determinations of the rate of decomposition could be made. The data cover a p_H range of from 2.0 to 11.0 and a temperature range of from 0 to 37 C., and they are presented in a series of graphs. When compared with a solution of the crystalline salt at p_H 2.0 and a temperature of 0 C., a partially purified solution of penicillin under the same conditions was found to be less stable. It appears that the destruction of penicillin in aqueous solution is an irreversible reaction of the first order. The time required to destroy a solution of crystalline sodium penicillin at p_H 2.0 and a temperature between —10 and 40 C. and the rate of destruction at any chosen point during that time may be calculated by the use of formulas derived from the data presented in this paper.

STOESSER, Minneapolis.

SULFAMETHAZINE: IN VITRO ACTION ON ENTERIC PATHOGENS AS COMPARED WITH SULFADIAZINE AND SULFAMERAZINE. FRITZ B. SCHWEINBURG and I. JACQUES YETWIN, J. Bact. **49**:193 (Feb.) 1945.

The authors had planned to test two new sulfonamide drugs, sulfapyrazine and sulfamethazine. They found the output of sulfapyrazine limited, and they therefore used the other sulfonamide compound, sulfamethazine. This substance is dimethylsulfadiazine and is consequently, related not only to sulfadiazine but to sulfamerazine, which is monomethylsulfadiazine. The studies which were carried out with sulfamethazine in vitro showed that the preparation was by far a more effective bactericidal and bacteriostatic agent against Eberthella typhosa, Escherichia coli and the Salmonella varieties than the other sulfonamide compounds examined. A similar conclusion was drawn by the authors in its use against Shigella sonnei and the Hiss dysentery strain. They found that the drug is effective in the test tube on the typhoid–colon bacillus group in concentrations which suggest that clinical application should be attempted, especially since all other sulfonamide drugs offer no convincing evidence of their ability to combat typhoid fever or of the chronic carrier state of the disease and infections with Salmonella.

STOESSER, Minneapolis.

EXPERIENCE WITH SULFAPYRAZINE IN CHILDREN. HARVEY N. VANDEGRIFT, J. Pediat. **25**:386 (Nov.) 1944.

1. Sulfapyrazine administered orally in a dosage of 1 grain (0.064 Gm.) per pound of body weight results in low blood levels which are therapeutically effective.

2. An increased dosage does not effectively raise the blood concentration.

3. Subcutaneous administration was effective.

4. Spinal fluid concentrations were found to equal from 50 to 60 per cent of the blood level.

5. The only toxic reactions found in 119 infants and ildren treated by sulfapyrazine were 1 instance of ross hematuria after intravenous administration (0.84 er cent) and 9 of transient microscopic hematuria 7.5 per cent).

AUTHOR'S SUMMARY.

ENICILLIN: ITS USE IN PEDIATRICS. WALLACE E. HERRELL and ROGER L. J. KENNEDY, J. Pediat. **25**: 505 (Dec.) 1944.

The results obtained following the use of penicillin the treatment of a variety of bacterial infections in cases in the pediatric age group have been reported. appears that satisfactory results were noted in 45 these 54 cases. It is evident also that the results mong children are as good as, if not somewhat better an, the results obtained after the use of penicillin in comparable group of infections of adults. This is nderstandable in view of the fact that overwhelming fections such as bacteremia and severe cellulitis carry, general, higher morbidity and mortality rates when ese diseases occur in the older age groups than when ey occur among children.

Penicillin has been used satisfactorily in the treatment bacteremia, severe cellulitis, acute osteomyelitis, eningitis, pulmonary suppurative disease, certain pyo- nic cutaneous infections, otitis media, actinomycosis nd a group of miscellaneous infections including septic rthritis and ocular infections in children.

On the basis of our present knowledge, penicillin is little or no value in the treatment of infections due to gram-negative bacilli; including undulant fever, tularemia, influenza or infections owing to the colon-typhoid-dysentery group of organisms or to Friedländer's bacillus. Infections of the urinary tract due to the gram-negative organisms mentioned do not respond to penicillin therapy. Penicillin is of little or no value in the treatment of infections of the urinary tract due to Streptococcus faecalis. It is of no value in the treatment of tuberculosis, acute rheumatic fever, rheumatoid arthritis, ulcerative colitis, malaria or blastomycosis; it is likewise of no value in the treatment of leukemia and of certain cutaneous diseases, including lupus erythematosus and pemphigus.

Penicillin possesses a distinct advantage over sulfonamide compounds in the treatment of infections of infants and children not only because of its greater antibacterial powers but also because of the extremely low incidence of toxic manifestations resulting from its use.

HERRELL, Rochester, Minn.

PENICILLIN AND STAPHYLOCOCCUS PYOGENES. JOSEPH W. BIGGIN, Irish J. M. Sc. November 1944, p. 553; December 1944, p. 585.

The authors state that penicillin is bactericidal for staphylococci but occasionally does not kill all of a broth culture. Persisting bacteria rarely exceed 1 per million and are believed to survive because they are in the nondividing or dormant form.

SNELLING, Toronto, Canada.

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Associação Paulista de Medicina, Secçaõ de Pediatrias

President: Dr. Vicente Lara.
First Secretary: Dr. Armando de Arruda Sampaio.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

British Paediatric Association

President: Prof. L. G. Parsons, 58 Calthorpe Rd., Five Ways, Birmingham.
Secretary: Dr. Donald Paterson, 27 Devonshire Pl., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandische Vereeniging voor Kindergeneeskunde

President: Dr. J. H. G. Carstens, Servaasbolwerk 14ª, Utrecht.
Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340, 's Gravenhage.
Place: Different places. Time: Three times a year.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. L. F. Meyer, 29 Toelsohn St., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

Royal Society of Medicine, Section for the Study of Disease in Children

President: Prof. Norman Capon, 49A Rodney St, Liverpool, England.
Secretary: Dr. J. N. O'Reilly, 46 Harley St., London W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

Sociedad Cubana de Pediatria

President: Dr. Teodosio Valledor Campo, Habana.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: Last Wednesday of every month.

Sociedad Ecuatoriana de Pediatria

President: Dr. Francisco de Icaza Bustamente.
Secretary: Dr. M. I. Gómez Lince, P. O. Box 69 Guayaquil.

Sociedad Mexicana de Pediatria

President: Dr. Fernando López Clares, 12/a. Medellin 191, Mexico.
Secretary: Dr. Jesus Gómez Pagola, Versalles 6 Mexico.

Sociedad de Pediatria de Córdoba

President: Dr. Juan Francisco Herrera, Córdoba Argentina.
Secretary: Dr. Bernardo Serebrinsky, Dean Funes 200 Esq. Ocaña (N.), Córdoba, Argentina.

Sociedad de Pediatría de Santiago de Cuba

President: Dr. Antonio Béguez César, Sagarra 10 Santiago de Cuba.
Secretary: Dra. Susana Texidó Vaillant, Padre Pi 57, Santiago de Cuba.
Place: Colegio Médico.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Sociedad Venezolana de Puericultura y Pediatria

President: Dr. Pedro J. Alvarez.
Secretary: Dr. Ernesto R. Figueroa, 3a Avenida 10, Bella Vista, Caracas.
Place: Hospital Municipal de Niños Jose Manuel de los Rios, Caracas.

Société de Pédiatrie de Paris

President: Dr. Leveuf, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

Uruguayan Society of Pediatrics

President: Dr. José Alberto Praderi, Eduardo Acevedo 1132, Montevideo.
Secretary: Dr. Héctor Fossatti, Durazno 1882, Montevideo.
Place: Club Medico del Uruguay, Avenida Agraciado 1464 (Piso 13), Montevideo.

NATIONAL

American Medical Association, Scientific Assembly, Section on Pediatrics

Chairman: Dr. John Aikman, 184 Alexander St., Rochester, N. Y.
Secretary: Dr. Gilbert J. Levy, 188 S. Bellevue Blvd., Memphis, Tenn.

American Academy of Pediatrics

President: Dr. Joseph S. Wall, 1864 Wyoming Ave. N. W., Washington, D. C.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Book-Cadillac Hotel, Detroit. Time: Jan. 15-18, 1945.
Region I. Place: Hotel Pennsylvania, New York. Time: April 2-4, 1946.
Region II. Place: Cincinnati, Ohio. Time: Nov. 14, 1945.

American Hospital Association, Children's Hospital Section

Chairman: Dr. Joelle C. Hiebert, 299 Main St., Lewiston, Maine.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly, Mass.

American Pediatric Society

President: Dr. C. Anderson Aldrich, Mayo Clinic, Rochester, Minn.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis 8.

Canadian Society for the Study of Diseases of Children

President: Dr. H. S. Little, 300 Dufferin Ave., London, Ontario.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, 67 College St., Toronto 2.

Society for Pediatric Research

President: Dr. Edward M. Bridge, 219 Bryant St., Buffalo, N. Y.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia 46.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Robert Alway, University of Utah School of Medicine, Salt Lake City 2.
Secretary-Treasurer: Dr. L. Paul Rasmussen, 1020 Boston Bldg., Salt Lake City 1.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. William P. Buffum, 122 Waterman St., Providence, R. I.
Secretary-Treasurer: Dr. James Marvin Baty, 1101 Beacon St., Brookline, Mass.
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. M. L. Bridgeman, 1020 S. W. Taylor St., Portland, Ore.
Secretary: Dr. C. G. Ashley, 833 S. W. 11th Ave., Portland, Ore.

Northwestern Pediatric Society

President: Dr. George B. Logan, 102 Second Ave. S. W., Rochester, Minn.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Rocky Mountain Pediatric Society

President: Dr. G. R. Fisher, 23 E. Pikes Peak Ave., Colorado Springs, Colo.
Secretary: Dr. Joseph H. Lyday, 1850 Gilpin St., Denver.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. William Weston Jr., 1428 Lady St., Columbia, S. C.
Secretary: Dr. Angus McBryde, 604 W. Chapel Hill St., Durham, N. C.

STATE

Alabama Pediatric Society

President: Dr. Jerome C. Chapman, 2160 Highland Ave., Birmingham.
Secretary-Treasurer: Dr. Ruth Berrey, 2021-6th Ave. N., Birmingham.

Arizona Pediatric Society

President: Dr. Vivian Tappan, San Clemente, Tucson.
Secretary: Dr. Hilda Kroeger, Arizona State Health Dept. (Maternal and Child Welfare Division), Phoenix.

Arkansas State Pediatric Association

Chairman: Dr. C. B. Billinsgsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

California State Medical Society, Section on Pediatrics

Chairman: Dr. Charles W. Leach, 2000 Van Ness Ave., San Francisco 9.
Secretary: Dr. Chester I. Mead, 1930 Truxton Ave., Bakersfield.

Florida State Pediatric Society

President: Dr. Ludo Von Meysenbug, Box 3356, Daytona Beach.
Secretary: Dr. Robert Blessing, 409 Blount Bldg., Ft. Lauderdale.
Place: Concurrent with state association meeting at time of convention.

Georgia Pediatric Society

President: Dr. Ruskin King, 10 W. Taylor St., Savannah.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Edward T. Wakeman, 129 Whitney Ave., New Haven.
Secretary: Dr. Herman Yannet, Southbury Training School, Southbury.
Time: Three meetings a year.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Craig D. Butler, 715 Lake St., Oak Park.
Secretary: Dr. A. J. Fletcher, 139 N. Vermilion, Danville.

Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Mark L. Floyd, Children's Hospital, Iowa City.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn, N. Y.
Secretary: Dr. George R. Murphy, 292 Madison Ave., New York.
Place: Same as State Society. Time: Same as State Society.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Secretary: Dr. P. F. Lucchesi, Philadelphia Hospital, Philadelphia.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Donald J. Barnes, 3001 W. Grand Blvd., Detroit, Mich.
Secretary: Dr. Mark F. Osterlin, Central Michigan Children's Clinic, Traverse City.
Place: Detroit. Time: September 1945.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

Nebraska Pediatric Society

President: Dr. John L. Gedgoud, University of Nebraska Hospital, Omaha.
Secretary-Treasurer: Dr. Gerald C. O'Neil, 640 City National Bank Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

New Hampshire Pediatric Society

President: Dr. MacLean J. Gill, 14 N. State St., Concord.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

North Carolina Pediatric Society

President: Dr. Arthur H. London Jr., 1105 W. Main St., Durham.
Secretary: Dr. Jay M. Arena, Duke Hospital, Durham.

Northern California Pediatric Society

President: Dr. John Mott Rector.
Secretary: Dr. George Bates, 490 Post St., San Francisco.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

Oklahoma State Pediatric Society

President: Dr. G. R. Russell, 604 S. Cincinnati Ave., Tulsa.
Secretary: Dr. Luverne Hays, 108 W. 6th St., Tulsa.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

South Carolina Pediatric Society

President: Dr. Lonita Boggs, 301 E. Coffee St., Greenville.
Secretary-Treasurer: Dr. Hilla Sheriff, 429 Wade Hampton Office Bldg., Columbia 10.

Texas Pediatric Society

President: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas.

Virginia Pediatric Society

President: Dr. L. E. Sutton Jr., Medical College Hospital, Richmond.
Secretary: Dr. Emily Gardner, 1100 W. Franklin St., Richmond 20.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. Andrew Amick, 1021 Quarrier St., Charleston.
Secretary: Dr. A. A. Shawkey, Professional Bldg., Charleston.

LOCAL

Academy of Medicine of Cleveland Pediatric Section

Chairman: Dr. Charles L. Ruggles, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Walter Heymann, 2103 Adelbert Rd., Cleveland.
Place: Cleveland Medical Library Bldg. Time: 8:15 p. m., October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. John M. Ross, 530 St. Claire Ave. W., Toronto, Canada.
Secretary: Dr. J. H. Ebbs, 13 Queen's Park, Toronto, Canada.
Place: Academy of Medicine. Time: Third Thursday of each month.

Bronx Pediatric Society

President: Dr. Jacob H. Turner, 121 W. 197th St., New York.
Secretary: Dr. Harry S. Pizer, 1726 Davidson Ave., New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Kenneth G. Jennings, 159 Midwood St., Brooklyn.
Secretary: Dr. Joseph Battaglia, 713 Bushwick Ave., Brooklyn 21.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of each month except May, June, July, August and September.

Buffalo Pediatric Society

President: Dr. A. Wilmot Jacobsen, 187 Bryant St., Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. Arthur W. Benson, 2 St. Pauls St., Troy.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and October.

Chicago Pediatric Society

President: Dr. Louis W. Sauer, 636 Church St., Evanston, Ill.
Secretary: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.
Place: Children's Memorial Hospital, 707 Fullerton Ave. Time: Third Tuesday of each month.

Cincinnati Pediatric Society

President: Dr. Theodore K. Selkirk, 3605 Edwards Rd., Cincinnati.
Secretary: Dr. John H. Hunt, Kemper Lane Bldg., Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. Robert A. Knox, 3701 Fairmount Ave., Dallas 4, Texas.
Secretary-Treasurer: Dr. Gladys J. Fashena, 4585 Belfort Pl., Dallas 4, Texas.
Place: Children's Medical Center: Time: 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. Philip J. Howard, 2977 W. Grand Blvd., Detroit, Mich.
Secretary: Dr. John C. Montgomery, 564 Fisher Bldg., Detroit 2, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., second Wednesday of each month, four meetings a year.

Fulton County Medical Society, Pediatrics Section (Atlanta, Ga.)

Chairman: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Secretary: Dr. Harry Lange, 478 Peachtree St. N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: College Inn, Houston. Time: Fourth Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Edwin H. Schorer, 1103 Grand Ave., Kansas City.
Secretary: Dr. H. E. Petersen, Kirkpatrick Bldg., St. Joseph, Mo.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Milo B. Brooks, 1033 Gayley Ave. W., Los Angeles.
Secretary-Treasurer: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Abraham M. Litvak, 1145 Eastern Parkway, Brooklyn.
Secretary: Dr. Harold Levy, 750 St. Marks Ave Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m fourth Monday of each month, October to Apri inclusive.

Medical Society of the County of Queens, Inc. Section on Pediatrics

Chairman: Dr. Meyeron Coe, 217-02-91st Ave., Queens Village, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144-38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. Harry A. Spigel, 2647 Connecticut Ave., Washington, D. C.
Secretary-Treasurer: Dr. Perry W. Gard, 2520 Woodley Rd., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

Memphis Pediatric Society

President: Dr. W. L. Rucks, 1074 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry J. Jacobson, 1193 Madison Ave., Memphis, Tenn.

Milwaukee Pediatric Society

President: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2.
Secretary-Treasurer: Dr. B. J. Malnekoff, 3213 N. Marietta Ave., Milwaukee 11.
Place: Milwaukee Children's Hospital. Time: Second Wednesday in February, April, June, October and December.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Alfred E. Fischer, 73 E. 90th St., New York.
Secretary: Dr. Robert O. Du Bois, 122 E. 76th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

Northern California Pediatric Society

President: Dr. John Mott Rector, 2000 Van Ness Ave., San Francisco.
Secretary: Dr. George Bates, 490 Post St., San Francisco 2.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

Oklahoma City Pediatric Society

President: Dr. William M. Taylor, 625½ N. W. 10th St., Oklahoma City.
Secretary: Dr. Jeanne Shotstall, 625½ N. W. 10th St., Oklahoma City.
Place: Oklahoma Club. Time: Third Thursday of each month.

Philadelphia Pediatric Society

President: Dr. Ruth Hartley Weaver, 1719 Rittenhouse St., Philadelphia.
Secretary: Dr. Sherman Little, 1740 Bainbridge St., Philadelphia 46.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p. m., second Tuesday in October, December, February and May.

Pittsburgh Pediatric Society

President: Dr. Elwood Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate months from October to June, inclusive.

Puget Sound Pediatric Society

President: Dr. D. M. Dayton, 740 St. Helens Ave., Tacoma.
Secretary: Dr. W. B. Chesley, 1306 Madison St., Seattle 4.
Place: College Club. Time: Third Friday of each month from September to June at 6:30 p. m.

Richmond Pediatric Society

President: Dr. T. Stanley Meade, 913 Floyd Ave., Richmond, Va.
Secretary-Treasurer: Dr. Edwin L. Kendig Jr., 828 W. Franklin St., Richmond 20, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month except June, July and August.

Rochester Pediatric Society

President: Dr. William L. Bradford, 260 Crittenden Blvd., Rochester 7, N. Y.
Secretary-Treasurer: Dr. Donald D. Posson, 222 Chili Ave., Rochester 11, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Joseph C. Jaudon, 337 N. Euclid Ave., St. Louis.
Secretary-Treasurer: Dr. Gilbert B. Forbes, 500 S. Kingshighway, St. Louis.
Place: Branscome Hotel. Time: 7:00 p. m., third Thursday of each month from November to June.

Southwestern Pediatric Society

President: Dr. William Belford, 420 Walnut St., San Diego, Calif.
Secretary: Dr. Robert J. Dostal, 710 Wilshire Blvd., Santa Monica, Calif.
Place: University Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Park Bradshaw, Muskegon, Mich.
Secretary: Dr. Harry A. Towsley, University of Michigan, Department of Pediatrics and Communicable Diseases, Ann Arbor, Mich.

Westchester County Medical Society, Pediatric Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: Hospitals of Westchester County. Time: Third Thursday in November, January, March and May.

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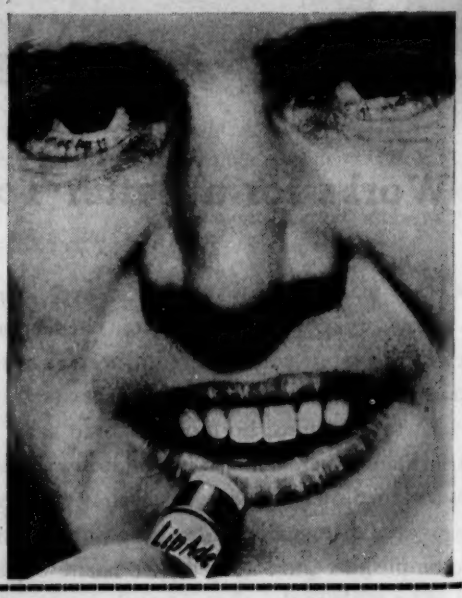

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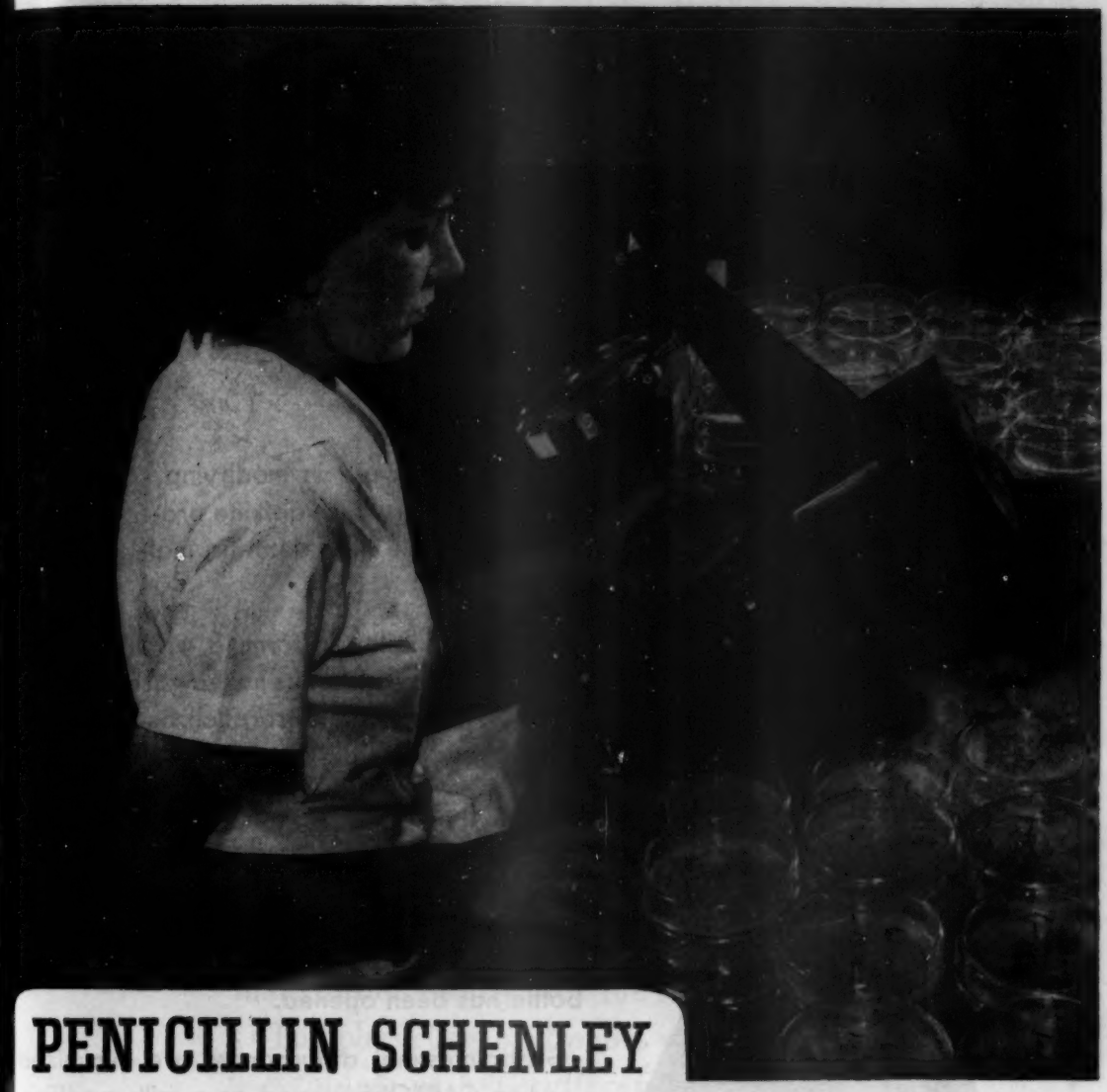

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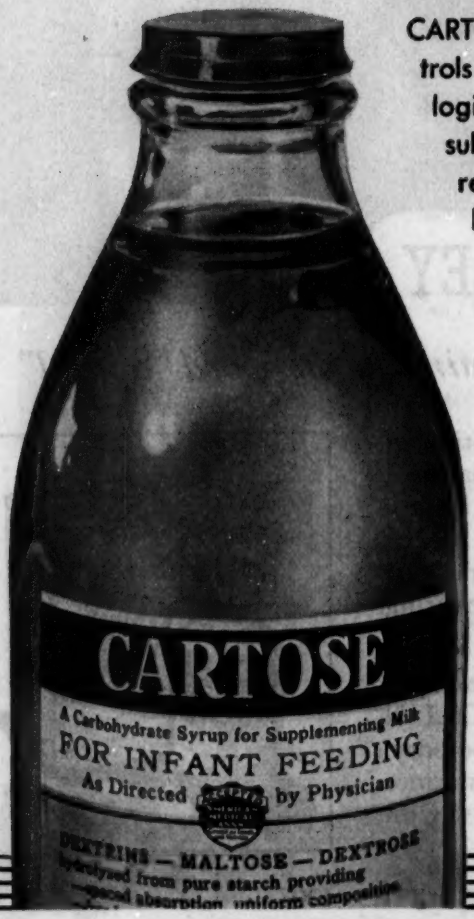

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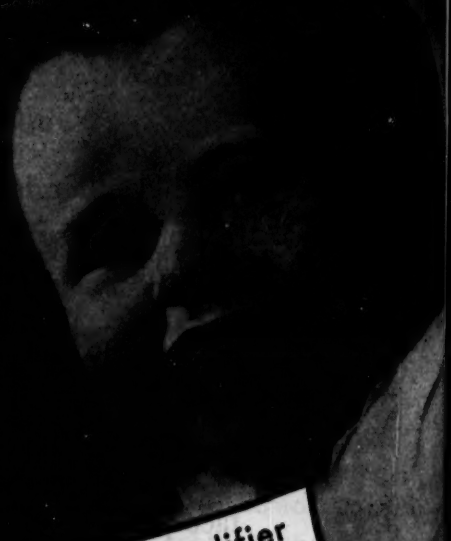

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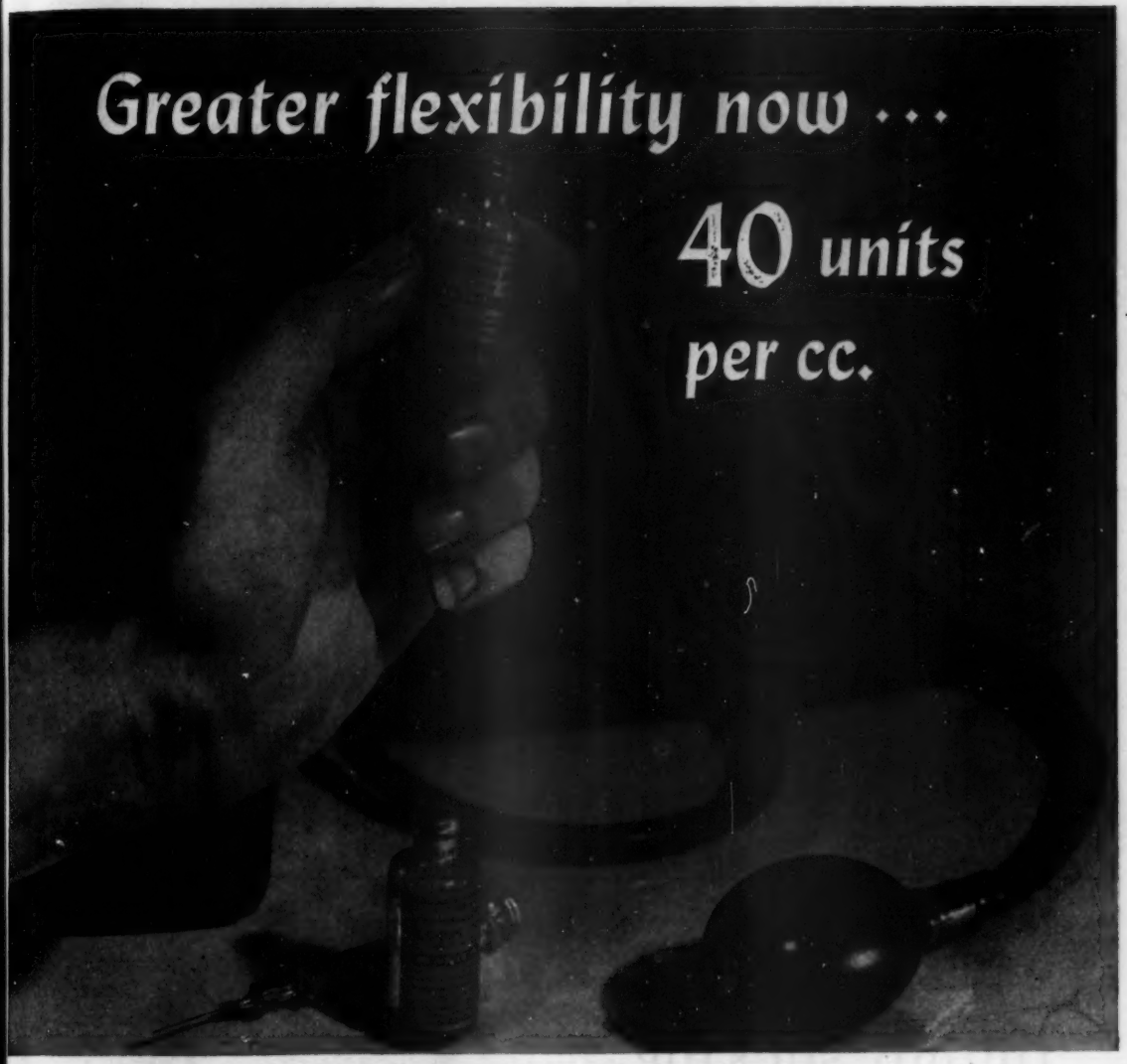

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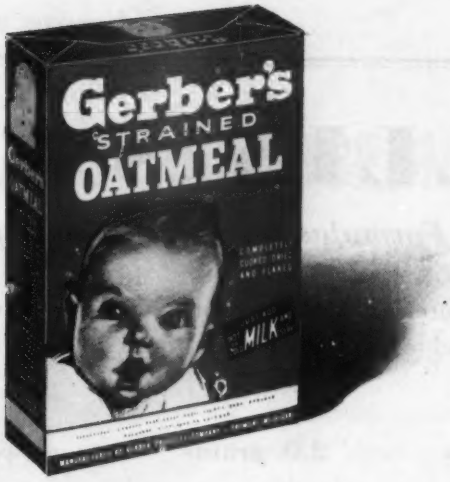

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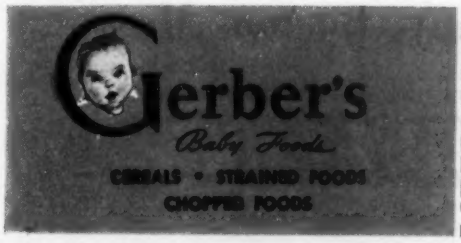

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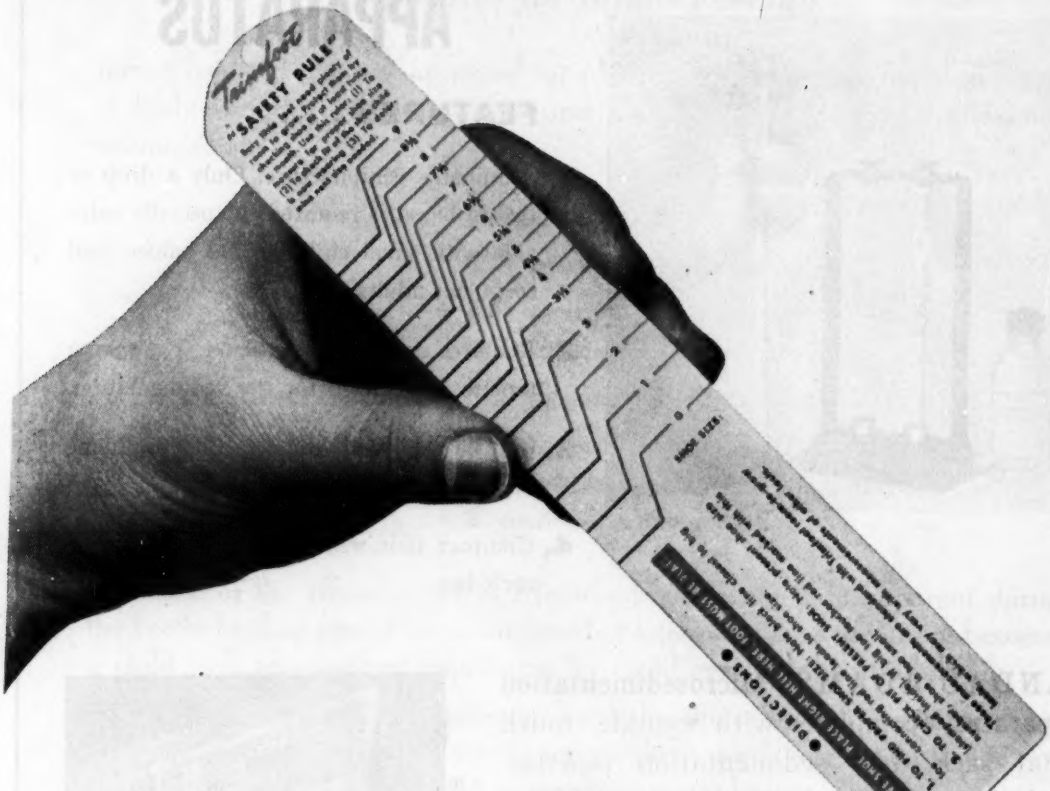

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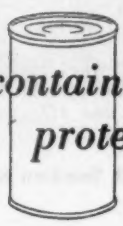

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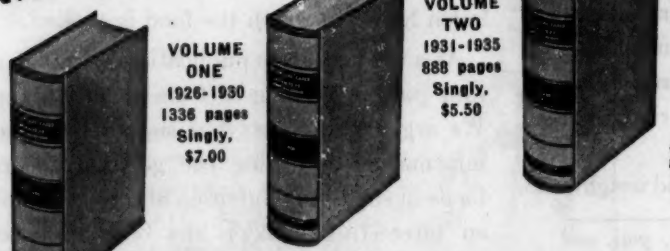

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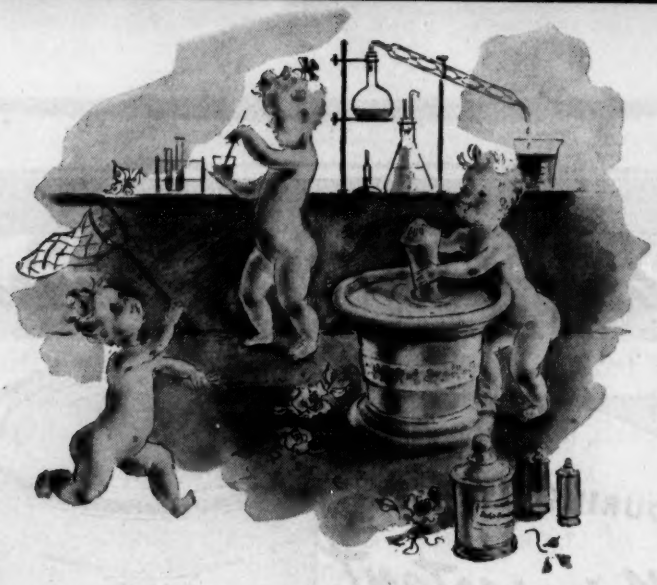

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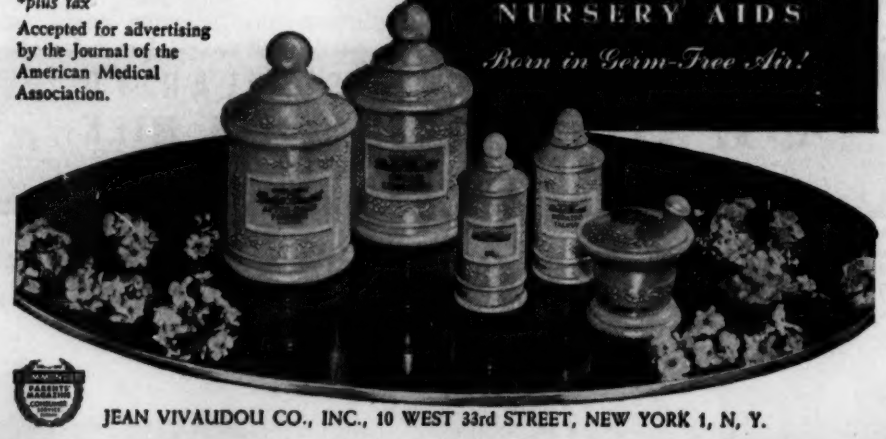

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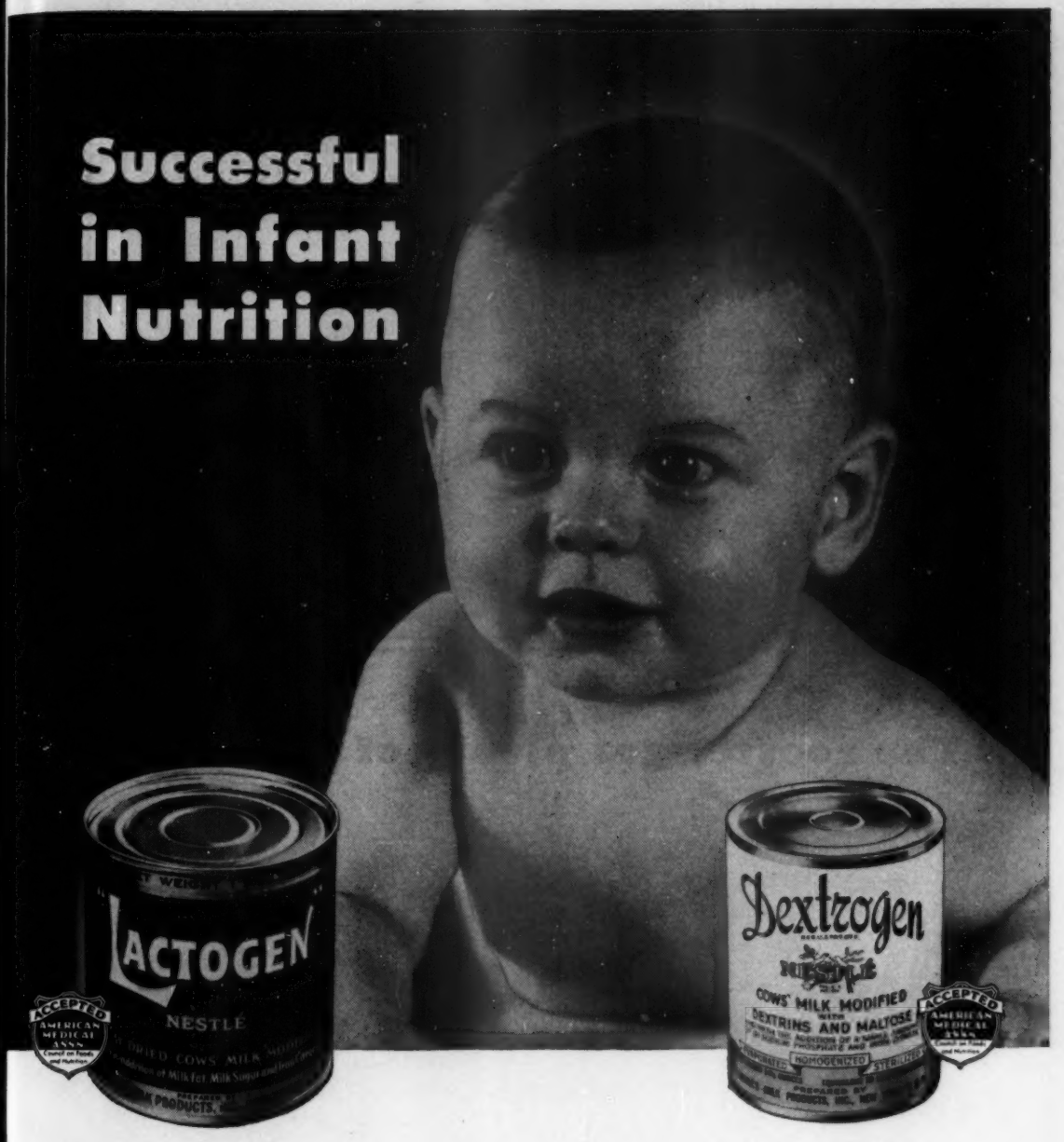

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